Is Testosterone Treatment Good for the Prostate? Study of Safety during Long-Term Treatment

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ABSTRACT

Introduction. For men with androgen deficiency on testosterone replacement therapy (TRT), clinical concern relates to the development of prostate cancer (PCa).
Aim. An updated audit of prostate safety from the UK Androgen Study was carried out to analyze the incidence of PCa during long-term TRT.
Main Outcome Measures. Diagnosis of PCa in men receiving TRT, by serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE), and its relation to different testosterone preparations.
Methods. One thousand three hundred sixty-five men aged 28–87 (mean 55) years with symptomatic androgen deficiency and receiving TRT have been monitored for up to 20 years. All patients were prescreened for PCa by DRE and PSA along with endocrine, biochemical, hematological, and urinary profiles at baseline and every 6 months. Abnormal findings or rising PSA were investigated by transrectal ultrasound and prostate biopsy. The data were compared for the four different testosterone preparations used in TRT, including pellet implants, Restandol, mesterolone, and Testogel.
Results. Fourteen new cases of PCa were diagnosed at one case per 212 years treatment, after 2,966 man-years of treatment (one case per 212 years). Time to diagnosis ranged from 1 to 12 years (mean 6.3 years). All tumors were clinically localized and suitable for potentially curative treatment. Initiating testosterone treatment had no statistically significant effect on total PSA, free PSA or free/total PSA ratio, and any initial PSA change had no predictive relationship to subsequent diagnosis of cancer.
Conclusions. The incidence of PCa during long-term TRT was equivalent to that expected in the general population. This study adds to the considerable weight of evidence that with proper clinical monitoring, testosterone treatment is safe for the prostate and improves early detection of PCa. Testosterone treatment with regular monitoring of the prostate may be safer for the individual than any alternative without surveillance. **Feneley MR and Carruthers M. Is testosterone treatment good for the prostate? Study of safety during long-term treatment. J Sex Med **;**:**–**.**

Key Words. Testosterone Replacement Treatment (TRT); Myth that TRT Causes Prostate Cancer; Long-Term Outcomes; Prostate Cancer; PSA; Testosterone Deficiency; Symptoms Scores; Early Diagnosis; Screening; Pellet Implants; Testosterone Undecanoate; mesterolone; Testogel; UK Androgen Study (UKAS)

Introduction

> The great enemy of the truth is very often not the lie – deliberate, contrived, and dishonest, but the myth, persistent, persuasive, and unrealistic. Belief in myths allows the comfort of opinion without the discomfort of thought. John F. Kennedy

The main concern limiting the introduction of testosterone treatment in men relates to the progression of undiagnosed prostate cancer (PCa) or its development with advancing age. This is despite the evidence from a number of published reviews, such as those by Morgentaler [1] and Roddam et al. [2], finding the notion that testosterone treatment causes PCa to be a myth. Similarly, Shabsigh et al. concluded from an extensive analysis of 44 studies that "none demonstrated that testosterone therapy for hypogonadism increased PCa risk or increased Gleason grade of cancer detected in treated vs. untreated men" [3].

However, fears about testosterone replacement therapy (TRT) inducing PCa remain the main reason why only a small percentage of the men who could benefit from testosterone treatment worldwide are actually treated with testosterone [4,5]. In the former study in 2006, it was found that about 68% of physicians associate use of testosterone more with risks than benefits, more so in Europe (73%) than elsewhere. The main reason quoted by 51% of physicians was the risk of PCa. When asked if their readiness to prescribe testosterone to elderly men would increase if authoritative scientific studies dismissed the fear that testosterone treatment would increase the risk of PCa and benign prostatic hypertrophy (BPH), the response was overwhelmingly "yes," in 62% from Europe and 74% elsewhere.

In a follow-up study in 2010, in spite of much more experience and many reassuring articles about TRT, concerns about possible side effects of the treatment were even more prevalent, especially in relation to PCa, which had risen to 55% [6].

The present study was designed as a prospective audit to address and inform attitudes to TRT. It describes long-term outcome with several different forms of treatment given to 1,365 patients for periods of up to 20 years—The UK Androgen Study (UKAS).

Methods

The UKAS is an ongoing analysis of the findings in one of the authors' (MC) clinical work in the Centre for Men's Health in London since it was established in 1989. Ethical permission for this audit was obtained from the St. Mary's Hospital Local Research Ethics Committee, with standard informed consent from the patients for use of their anonymized data. The consent included a warning that the treatment might, according to the data information sheets, possibly cause or accelerate PCa, produce temporary infertility, or cause other side effects such as rashes in the case of testosterone gels.

The patients were self-selected men who presented for evaluation of symptoms of testosterone deficiency syndrome (TDS). Of these 1,771 men, 406 made one visit only (mean age 54 years, range 25–89 years), and 1,365 men were diagnosed with TDS. This group was treated with testosterone for at least 3 months, and up to 20 years, as shown in Figure 1, mean age being 54.2 (range 24–88) years, 93% being white.

A standardized general medical history was taken, especially focused on factors that might be related to androgen deficiency such as diabetes, cardiovascular disease, stress, alcohol, and medications. As well as examining the genitalia, general physical examination including digital rectal examination (DRE) was performed. Blood pressure, pulse rate, and anthropometry were carried out before and during treatment.

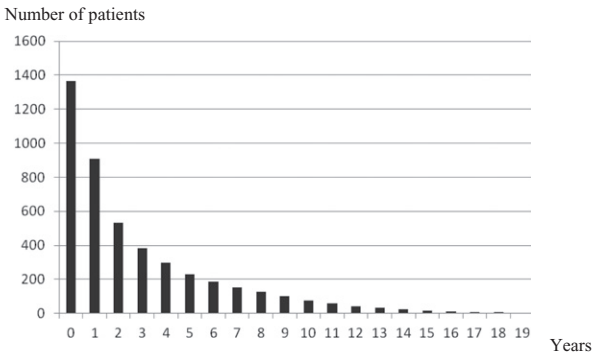

Figure 1 Flow chart of patients in UK Androgen Study. (Number of patients on follow-up—years from recruitment).

Often symptoms of testosterone deficiency, including loss of libido and energy, erectile dysfunction (ED), loss of morning erections, night sweats, joint pains, depression, irritability, and impaired memory, had been present for 3–5 years prior to attending the clinic for the first time.

Although treatment within this clinical practice could not be blinded, and bias in the subjective reporting cannot therefore be excluded, every effort has been made to make the observations as objective as possible. First visit data served as the control in each patient, for comparison with data from subsequent visits, which were usually at 6 monthly intervals once treatment had been optimized in terms of symptomatic response.

To establish the initial diagnosis of testosterone deficiency and to monitor response to treatment, a detailed testosterone deficiency symptom scale, the Andropause Check List [7] was completed at each visit and found to correlate closely with the similar Aging Male Symptom (AMS) scale [8]. Full endocrine, biochemical, and hematological profiles were available to guide treatment and monitor its safety, together with the clinical and physiological data also recorded at each of the 6 monthly visits.

Exclusion Criteria

As the intention was to study the diagnosis and treatment of secondary testosterone deficiency, certain groups of patients were excluded:

1. Primary testosterone deficiency, e.g., cases with a history of nondescent of testes, bilateral orchidectomy, or patients diagnosed as Klinefelter's syndrome;
2. Prostate or breast cancer, or when PCa was suspected in men with a raised prostate-specific antigen (PSA) (>4 ng/mL) or abnormal DRE, and referred elsewhere for further investigation;
3. Asymptomatic men attending for general medical screening;
4. Men seeking physical fitness training. Anabolic steroid treatment is not offered at the clinic to young men seeking improvement in athletic performance or physique;
5. Young men with "locker room syndrome"—defined in this study as a fixation, usually starting in adolescence, on having an inadequately sized penis;
6. Men diagnosed as "Male Mid-life Crisis" [9]—a psychological existential crisis usually starting ages at 35–45 years of age; and
7. Patents with a primary diagnosis of depression.

For the last 12 years, laboratory data have been provided by Quest Laboratories and entered directly into an Access database via secure electronic data link, to prevent transcription errors. Blood samples were taken fasting between 9 and 11 AM to minimize the variables that can otherwise invalidate androgen assays [10] and to get a clearer picture of changes in lipid and carbohydrate metabolism with treatment.

The endocrine profile included total testosterone (TT), sex hormone binding globulin (SHBG), calculated free testosterone (cFT), estradiol (E2), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). cFT was determined using the Vermeulen formula [11]. Details of the very varied endocrine background provided by the different treatments will be reported elsewhere.

Using samples taken prior to digital or ultrasound transrectal examination, total and free PSA, giving the free/total ratio, were measured on the Immulyte 1,000 Analyser (Siemens Healthcare Diagnostics Inc. Tarrytown, NY USA) until 10 years ago, and then the Beckman Access Analyser (Beckman Coulter Inc, Brea, CA, USA). The biochemical profile included standard renal function tests and estimated glomerular filtration rate, liver function tests, uric acid, iron, fasting glucose, triglycerides, and total cholesterol, together with high density lipoprotein (HDL) and low density lipoprotein (LDL). The hematology profile included hemoglobin and indices to exclude polycythemia, white cell count and differential, platelets, and erythrocyte sedimentation rate. Routine urine chemistry was also performed.

The study was initiated in 1990, before guidelines such as those of Wang et al. [12] had been established. For consistency, patients were therefore diagnosed with TDS based on clinical assessment, symptom score, and to a lesser extent the detailed endocrine profile. Most patients had TT levels of less than 14 nmol/L, or if the cFT was low due to a high SHBG, with characteristic symptoms of TDS, a 3-month therapeutic trial was offered.

Various testosterone preparations were used to achieve symptom response, including pellet implants (TI; Organon, Organon Laboratories, Cambridge, UK), oral testosterone undecanoate (TU; Restandol, Organon), mesterolone (ME; Proviron, Bayer, Bayer PLC, Newbury, Berks, UK), and testosterone gel (TG; Testogel, Bayer). Some patients changed treatment preparations to achieve satisfactory remission of symptoms.

It is appreciated that there are several unavoidable potential sources of bias. First, the findings could be biased toward cases that respond well clinically, and therefore continued on treatment. However, as far as possible, patients who did not respond to their initial treatment in doses titrated against symptoms were provided with another preparation that gave the required relief.

Second, a general medical approach to treatment was used, with advice and encouragement where needed in relation to reducing stress, alcohol, and weight, as well as increasing physical activity and other lifestyle modifications. Some of these goals were often difficult for the patient to achieve and maintain even with the improved mood and energy induced by testosterone treatment. Also, where there were other clinical conditions needing intervention, such as hypertension, hyperlipidemia, or diabetes, the additional treatment given may have distorted the response attributable to testosterone alone.

Third, the patients did not live in a controlled and stable experimental setting, and over the many years of treatment, they and their partners could be subject to major life events that may in some cases have influenced their responses to the particular form of testosterone being taken at the time. Such major life events included relationship breakups, job losses, retirement, major illnesses, and bereavement. In general, however, these extraneous influences would be nullified by the large number of cases studied.

The data were collated using a computerized practice management system called the Global Andrology Assessment and Treatment Tracking program (GAATT), developed specifically for use in the Centre for Men's Health. This program assembled the information on all patients in an Access (Microsoft) database, and then extracted it using a data mining program, by which individual or group responses to treatment could be assessed. Statistical tests were performed using PASW (PASW18, SPSS (UK) Ltd. Woking, Surrey) (SPSS) 18 statistics program. Results for PSA and endocrine data were log transformed for analysis, because it is now recognized that as with most endocrine data, their distribution is skewed and must be normalized for their analysis [10,13].

Screening for PCa

Men diagnosed with symptomatic TDS were screened for PCa at initial assessment, prior to consideration of TRT. Prostate assessment included urological history and serum PSA taken before DRE. All patients were informed of potential risks associated with undiagnosed early stage PCa, its development with advancing age, and the possible effect of testosterone on progression of prostate malignancy.

A family history of PCa was sought in the medical history and incorporated into any discussion with the patient of the risks of TRT and where relevant the need for biopsy, although this was not mandated by the history. Other than the one patient with a twin brother who had PCa, and underwent biopsy even with a normal PSA, no other patients who developed PCa had a family history of this.

Men with abnormal DRE suspicious for cancer were referred for further investigation and excluded from testosterone treatment. After initiating TRT, PSA was measured at 3 months, and thereafter every 6 months. DRE was not repeated unless lower urinary tract symptoms (LUTSs) developed, the PSA became abnormal, there was a trend of increasing PSA, or a decrease in free/total PSA ratio requiring further investigation.

Elevated PSA (total PSA > 4.0 ng/mL) was investigated by transrectal ultrasound and prostate biopsy. In some cases when PSA levels were >4.0 ng/mL, the decision to biopsy took into consideration PSA density, calculated as PSA in ng/mL divided by prostate volume in cc, where >0.15 ng/mL/cc was used as threshold for biopsy, and age where a PSA threshold >6.5 ng/mL was used in men over 70 years, together with the decision of the individual patient after consultation. Where needle biopsy was carried out, between 6 and 11 cores were taken according to contemporaneous practice.

Results

Endocrine Changes

All preparations used produced highly significant changes in endocrine values ($P < 0.0001$) between baseline and after 1 year, which were maintained over the remaining duration of the treatment periods.

TI caused sustained rises in TT and cFT levels, with marked suppression of LH and FSH levels, a small decrease in SHBG, and a slight increase in E2 levels.

TU caused a slight increase in TT, and cFT, mainly due to a large reduction in SHBG, with small decreases in E2 ($P = 0.001$), LH, and FSH.

ME caused a marked reduction in both TT and E2, with only slightly reduced cFT, SHBG, FSH and LH. TT was reduced ($P = 0.012$), with no change in cFT ($P = 0.531$) in spite of reduced SHBG, while E2 was markedly decreased.

TG gave marked rises in TT, cFT, and E2 and a clinically insignificant decrease in SHBG ($P = 0.042$), with raised E2, while LH and FSH levels were markedly suppressed.

There was no difference in PSA changes or distribution of PCa cases in the various treatment groups, or relation between initial and treatment endocrine levels and the development of PCa.

PSA and Age Distributions

The distribution of PSA values was skewed to the left (Figure 2A) and normalized by log-transformation (Figure 2B). Using log-transformed normalized data, the trend in total PSA with time on treatment was not statistically significantly different from the PSA relation to age at baseline (Figure 3). A similar trend was seen for free PSA and free/total PSA ratio with time (data not shown). No statistically significant change in total PSA or free/total PSA ratio was found at first follow-up after initiating treatment, and furthermore, any initial change had no predictive value for PCa.

Screening and Monitoring

Of the 406 men who made one visit only, 43 (10.6%) had a PSA > 4.0 ng/mL (PSA range 13.0–

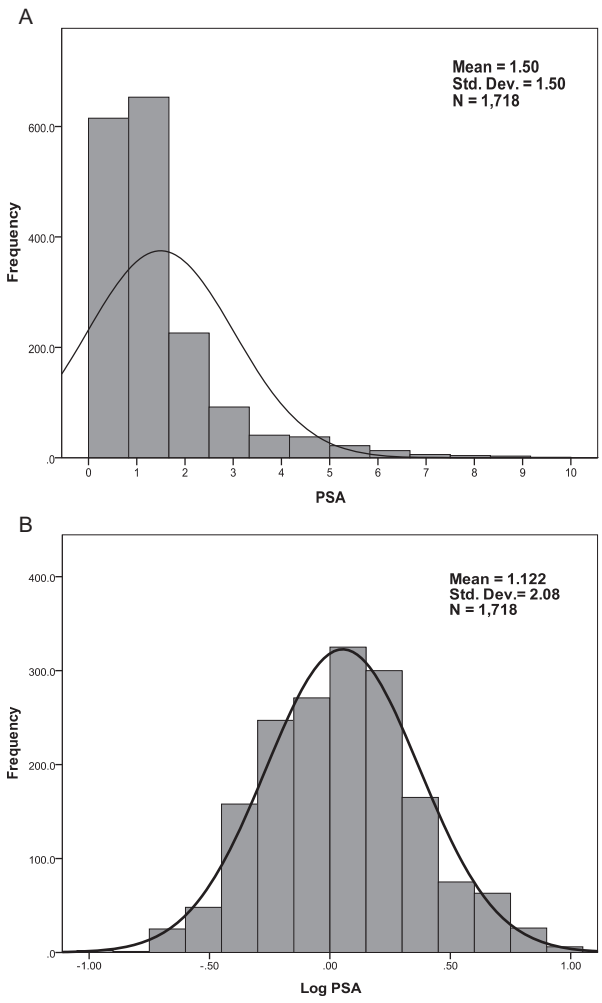

Figure 2 (A) Distribution of PSA levels at presentation (ng/mL). (B) Distribution of PSA levels at presentation after log transformation (base 10). PSA = prostate-specific antigen.

231 ng/mL). Although none of these men had formal follow-up, eight (2.0%) reported back that they had been diagnosed with PCa.

Of the 1,365 men given TRT, 1,200 men had normal PSA throughout their follow-up. Twenty-eight of these had transrectal ultrasound of the prostate, all indicating benign prostatic disease. As investigated by transrectal ultrasound (TRUS) with normal DRE and normal PSA level failed to identify any cases with PCa, and because the investigation has been recognized as being insensitive and nonspecific, it was routinely performed as a baseline investigation for only a limited period early in the study.

Four men with normal PSA and DRE had prostate biopsy, either for TRUS abnormalities or because they requested it as a baseline screening test. Among these, one case of PCa was diagnosed (PSA 3.1 ng/ml), only investigated because his twin had recently developed the condition.

Investigation of Elevated PSA

In the 1,365 treated men, 165 had at least one PSA > 4.0 ng/mL, either before or during treatment. They included 57 (4.2%) with initial PSA > 4.0 ng/mL, and of these, four (7.0%) developed PCa. Among 108 (7.9%) who developed PSA > 4.0 ng/mL after prior normal PSA, nine (8.3%) developed PCa.

Thirty-four men had prostate biopsy for elevated PSA, and among these, 13 men were diagnosed with cancer and 21 men had negative biopsy. Thirty men had a single PSA elevation and were lost to further follow-up. In many of the remaining 101 men, biopsy was considered unnecessary in the clinical context.

Of the 101 men who had one or more PSA level > 4.0 ng/mL and follow-up but no biopsy, 51 men had a PSA level that decreased to ≤4.0 ng/mL. Of the 50 men with more than one PSA level > 4.0 ng/mL, 20 men had PSA level considered normal for age (i.e., >4.0 and ≤6.5 ng/mL in men aged >70 years), including eight of those whose PSA reverted to ≤4.0 ng/mL; 27 men had normal PSA density (<0.15), including four of those with normal PSA for age, and eight of those whose PSA reverted to ≤4.0 ng/mL; 13 men had stable PSA (range 4.3–9.3 ng/mL) on serial surveillance including five men having TRUS showing benign changes only (PSA range 5.2–9.3 ng/mL); one man aged 89 years had a PSA rise

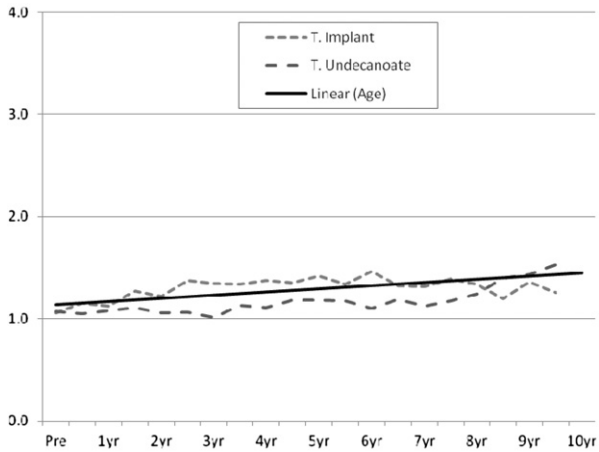

Figure 3 Total PSA (ng/mL) (logged means) during 10 years of treatment with pellet implants (TI) and oral testosterone undecanoate (TU), compared with age-related changes alone. PSA = prostate-specific antigen.

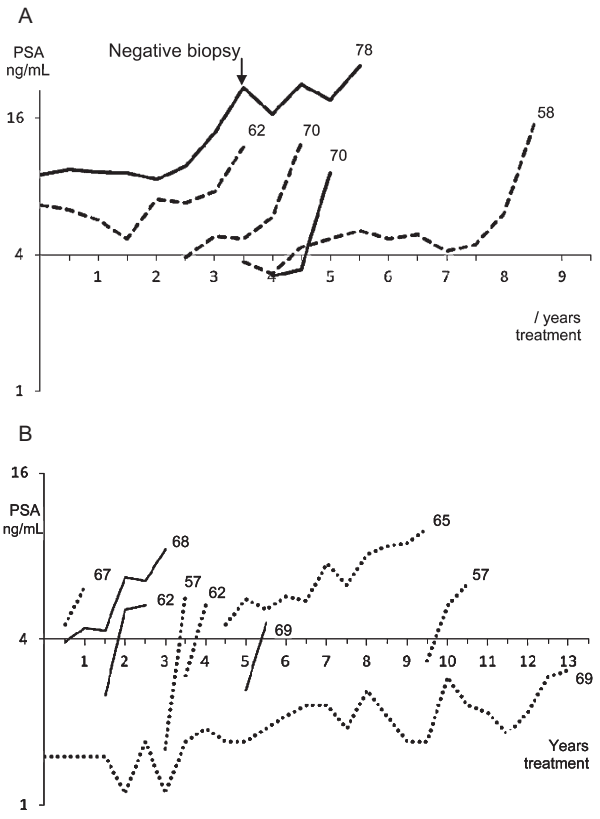

Figure 4 (A) PSA trends leading to diagnosis for patients with high (——) and intermediate risk (– – –) PCa, indicating age at diagnosis. (B) PSA trends leading to diagnosis for patients with low risk PCa, and either ≥3 positive cores (——) or <3 positive cores (·····), indicating age at diagnosis. For clarity, PSA values within a normal series after initiating TRT are not shown. PCa = prostate cancer; PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

to 24 ng/mL and was then lost to follow-up; nine men were referred to a urologist for investigation where biopsy was not carried out, and of these seven continued on treatment with stable PSA levels, and two men were lost to follow-up.

Assessment of PCa Cases

Fourteen cases of PCa were diagnosed in men between 57 and 78 (mean 66) years of age, after 1–12, (mean 6.3) years of testosterone treatment. In most of these cases, diagnosis was preceded by a clinically significant rise in PSA (Figures 4A,B). Unlike cancers diagnosed on prescreening, all were clinically localized based on clinical and radiological staging. The majority of men diagnosed with PCa had used more than one variety of androgen treatments. At the time of PCa diagnosis, six men were on TU (1,560 treatment years), four men were on TI (800 treatment years), two men on ME (297 treatment years), and two men on Testogel (309 treatment years). Therefore, the risk of developing PCa was not statistically significantly different between androgen preparations.

Among the 14 cases of PCa (Table 1a,b), two were considered high risk, based on Gleason Grade and PSA. Both were localized based on staging investigation, 1 being clinical stage T2 (i.e., a palpable abnormality confined within the prostate on DRE) and the other clinical stage T1c (i.e., nonpalpable). Both were treated with curative intent by radiotherapy in combination with neoadjuvant and adjuvant testosterone suppression.

Of the remaining 12 patients, all had Gleason Grade < 4, and all were clinical stage T1c (Table 1a,b). Among these, three had 3 or more cores involved and PSA < 10.0 ng/mL, and nine had fewer than 3 cores involved. Six men had fewer than 3 cores involved with maximum Gleason Grade 3 and PSA less than 10 ng/mL. Two men had only a single focus of cancer in one core only (ungraded).

All cases of PCa were suitable for treatment with curative intent. Follow-up was incomplete, with treatment by radiotherapy in six cases, radical prostatectomy in one case, active monitoring in two cases, and in five cases management was unknown.

Free PSA and Free/Total PSA Ratio

A further indication of the intrinsic safety of all forms of TRT was that with each preparation, the free PSA increased in proportion to the total PSA, so that the free/total ratio remained constant or increased with treatment (Table 2). Published studies indicate that a low ratio can indicate an increased risk of PCa, and may be a useful clinical index for PCa [14,15]. In this study, some reduction in this ratio was observed in those cases that developed PCa, changing from 0.23 to 0.17 between presentation and the time of diagnosis. Half the cases had low mean ratios (<0.10) for up to 3 years before the clinical diagnosis was made, supporting the suggestion that a low free PSA ratio may be actually be predictive for PCa [16].

Discussion

Limitations in assessment of PCa risk in this study arise from: (i) the absence of a baseline biopsy evaluation, though the follow-up data provided by this study suggests that this would be unnecessary in the great majority of patients, notwithstanding

Table 1a Details of PCa cases arising during treatment, at diagnosis, and their assigned risk

Risk category	High	High	Intermediate	Intermediate	Intermediate	Low	Low	Low	Low	Low	Low	Low	Low	Low
Gleason Grade	4 + 5	4 + 4	3 + 3	3 + 3	Focus	3 + 2	3 + 3	3 + 3	2 + 2	3 + 3	3 + 3	3 + 3	3 + 3	Focus
PSA at diagnosis (ng/mL)	27.1	9.2	15.0	12.4	11.9	4.6	8.4	5.3	6.2	5.8	5.3	6.3	3.1	10.0
PSA density (ng/mL/cc)	0.27	0.24	0.27	0.25	0.08	0.10	0.37	0.27	0.24	0.15	0.09	0.07	0.04	0.19
Clinical stage	T2	T1c	T1c	T1c	T1c	T1c	T1c	T1c	T1c	T1c	T1c	T1c	T1c	T1c
Age at cancer diagnosis (years)	78.2	70.6	58.1	70.9	62.7	69.3	68.4	62.2	67.2	57.5	62.5	57.9	69.7	65.2
Years of treatment	7.0	5.1	10.4	6.1	3.3	5.6	2.9	8.1	1.1	4.3	2.8	9.3	12.3	9.6
Initial PSA (ng/mL)	9.0	4.8	2.2	2.6	6.6	1.9	3.7	1.5	5.9	1.4	1.89	1.4	1.5	3.5

PSA = prostate-specific antigen; PCa = prostate cancer

Table 1b Distribution of prostate cancer risk and biopsy core involvement

	Low risk Gleason 3 + 3 or microfocus PSA < 10	**Intermediate risk** Gleason 3 + 3 or microfocus PSA > 10 and <20	**High risk** Gleason 4 + 4 or Gleason 4 + 5
Number of cases: all cancers	9	3	2
Number of cases: fewer than 3 cores involved	6	3	0

All cases presented as clinically organ confined disease.
PSA = prostate-specific antigen

the risks of biopsy related complication; (ii) biopsy was not carried out according to a prospective mandatory protocol in relation to the specified PSA-related thresholds; (iii) some patients becoming eligible for biopsy on TRT were lost to follow-up; and (iv) assessment of PCa risk was subject to contemporaneous biopsy protocols and may not necessarily reflect current strategies for predicting disease risk.

Within these limitations, inherent in an observational clinical study starting 20 years ago, the findings can be taken to indicate that with careful monitoring, men with TDS can be treated safely with marked and sustained reduction of their symptoms, and benefit to their quality of life, without increased risk of PCa. The detection rate for cancer in this study (one case per 212 man-years treatment), represents a somewhat lower risk than the age specific incidence of PCa in men aged 65–69 in the United Kingdom, which is more than 500 cases per 100,000 [17], notwithstanding that in those men diagnosed with cancer on TRT, all had early clinical stage disease and were potentially curable.

When undertaking TRT, the risk of underlying PCa or its development on therapy must be understood by the physician and patient alike. Benign hyperplasia and inflammatory prostatic disease are common in men with androgen deficiency, and these conditions contribute to PSA variation, particularly with urinary infection. In this study, analysis of the effect of initiating testosterone therapy on first follow-up PSA compared with baseline indicated no significant change; furthermore, it had no predictive value for PCa.

After testosterone treatment, 165 of 1,365 men (12.1%) had one or more PSA measurements >4.0 ng/mL. The overall biopsy rate in this study was reduced in part by consideration of PSA density and using a higher PSA cutoff in men over 70 years (>6.5 ng/mL). This would potentially reduce the total number of cancers detected, particularly those at an early pathological stage. Conversely, a PSA of 4.0 ng/mL or less does not rule out the possibility of clinically significant PCa that would be expected to progress if untreated.

One hundred thirty-five men with minor PSA elevation received ongoing testosterone treatment with clinical and biochemical follow-up. In the 34 men who had biopsy for elevated PSA, 13 men were found to have PCa. In this study, biopsy demonstrated cancer in one of four men with normal PSA who elected to have biopsy on account of testosterone therapy and a twin brother just diagnosed with PCa.

The overall cancer detection rate is substantially less than would be expected in a screening study, representing 38.2% (13/34) of men having biopsy for elevated PSA but only 20.6% (34/165) of men with PSA > 4.0 ng/mL. For comparison, in the European Randomized Study of Screening for Prostate Cancer, 162,243 men aged 55–69 years

Table 2 PSA changes between pretreatment levels and those at end of study period, together with PSA velocity on the different forms of testosterone treatment

Treatment	Duration of treatment (years)	Total PSA Pre-(ng/mL)	Total PSA End-(ng/mL)	Free PSA Pre-(ng/mL)	Free PSA End-(ng/mL)	PSA ratio Pre-(free/total)	PSA ratio End-(free/total)	PSA velocity (ng/mL per year)
Restandol	10	1.11	1.57	0.239	0.225	0.215	0.143	0.046
Pellet implants	10	1.18	1.44	0.227	0.287	0.193	0.200	0.026
Proviron	5	1.23	1.01	0.220	0.233	0.179	0.231	0.054
Testogel	5	1.09	1.37	0.252	0.348	0.231	0.254	0.070
Age alone	**10**	**1.28**	**1.74**	**0.280**	**0.386**	**0.220**	**0.221**	**0.047**

PSA = prostate-specific antigen

were investigated over a median follow-up period of 9 years, with cumulative incidence of PCa of 8.2% in the screening group and 4.8% in the control group [18]. By considering biopsy only for men where PSA was persistently elevated (i.e., did not return to normal on retesting), with PSA density exceeding 0.15 and/or PSA exceeding 6.5 ng/mL in men >70 years, 78 of 135 men were excluded from the requirement for biopsy. Another nine were referred to independent urologists who recommended not to biopsy on clinical grounds, of whom seven had further follow-up with stable PSA.

Clinical practice in this study contrasts the more aggressive diagnostic approach used in PCa screening studies. Had biopsy been taken in all men with a PSA > 4.0 ng/mL, or even in all men not fulfilling the modified exclusion criteria adopted in this study, a three- to fivefold greater cancer detection rate might have been anticipated. Intensive screening, particularly in an aging population, inevitably carries a substantial risk of detecting either clinically insignificant cancer, defined as disease that would not threaten the quality or duration of the individual's life [19]. Even among the cancers detected by the less rigorous criteria used in this study, 42.8% (6/14) cancers detected were pathologically insignificant based on the biopsy samples and contemporary Epstein criteria (clinical stage T1c, PSA density <0.15 ng/mL/cc, biopsy Gleason sum score ≤6, cancer in fewer than 3 cores and not more than 50% in any one core [20]).

Among the 14 cancers diagnosed on testosterone treatment, the majority (N = 9) were categorized as low risk (Gleason Grade ≤ 3, PSA < 10 ng/mL, and clinical stage T1c), including six pathologically insignificant by contemporary Epstein criteria. Three cancers were categorized as intermediate risk on account of a single PSA above 10 ng/mL; of these, two were Gleason sum score 3 + 3, and one had an ungradable microfocus associated with normal PSA density, which was categorized as pathologically insignificant. Two cancers were categorized as high risk based on Gleason Grade > 4 (Table 1a,b).

A growing literature suggests that high levels of androgens within the normal reference range decrease aggressive PCa risk. Similarly, high-grade PCa has been associated with low plasma testosterone [21]. In some studies of patients having radical prostatectomy, TT has been shown to be an independent predictor of extraprostatic disease; and with lower testosterone levels, the likelihood of nonorgan confined disease may be increased,

along with the risk of positive surgical margins [22]. There are however recent conflicting reports that preoperative TT is not a predictor of high-risk PCa or positive surgical margins at open radical prostatectomy [23,24].

There are many lines of evidence to support the statement that "the available evidence strongly suggests that TRT is safe for the prostate" [25]. Further evidence of this statement has been provided by a study on a large prospective cohort of 10,049 men, which contributed to the gathering evidence that the long-standing "androgen hypothesis" of increasing risk with increasing androgen levels can be rejected [26]. Supporting the safety of TRT, no significant change in median prostate tissue levels of testosterone and dihydrotestosterone were reported with testosterone treatment, in a 6-month placebo-controlled trial of 44 men, aged 44–78 years. Also, no treatment-related change was observed in prostate histology, tissue biomarkers, gene expression, cancer incidence or severity [27].

A lively debate on "Is testosterone a friend or foe of the prostate?" in this journal a year ago [28] combined expert opinion with a critical review of the currently available literature and found that there is no conclusive evidence that TRT "increases the risk of PCa or even prostatic hyperplasia." Also, reassuringly, higher endogenous TT and FT, and factors known to be associated with them such as sexual activity, have been found to be protective against PCa [29].

Other evidence supporting the safety of TRT includes, first, the worldwide clinical experience of physicians prescribing long-term treatment to young men with bilateral absent or malfunctioning testes. In such cases of life-long treatment, PSA levels remain comparable with the normal population range, and PCa is very rarely reported. In the author's experience with three such patients who had pellet implants for 58, 48, and 37 years, normal PSA levels were maintained over the last 10–20 years of treatment.

Second, there is evidence from the 'Yellow Card—Adverse Reactions Reporting System' in the UK [7]. Over 40 years, this reported a total of 214 reactions in 185 patients with only three deaths, only two of which might have been related to PCa (Table 3).

Third, short- and long-term studies on each testosterone preparation in current use have shown their safety in not increasing PSAs beyond the normal adult range. This includes TU [30–32], TI [33,34], MI [35], Testogel [36,37], and Nebido (Bayer PLC) [38,39]. In this study, the risk of PCa was equivalent for all preparations, and in particular, MI, which is known to increase serum dihydrotesterone (DHT) up to sixfold, was not associated with a greater PCa risk.

Finally, the present large-scale and relatively long-term study of 2,966 man-years treatment with four different forms of testosterone, giving widely differing endocrine profiles, shows no increased cause for clinical concern in relation to the prostate. There was no increase in PCa rates above that which would be expected in the general population at the same age, and no significant changes in PSA trend above that associated with age. This is most clearly seen in a comparison of the log means of total PSA over 10 years of treatment with TI and TU and the rise attributable to age alone (Figure 3).

DHT is often considered the most active androgen affecting the prostate, and benign enlargement is frequently treated with 5α-reductase inhibitors. Recent studies suggest that these may reduce the progression of benign prostatic hyperplasia as well as PCa, although high-grade cancer remains a concern [40–42]. Other studies indicate that circulating DHT levels and treatment with DHT do not affect the level of this hormone within the prostate [43].

In considering the benefits of TRT in men, there are parallels to treatment of estrogen deficiency in menopausal women, not only in the symptomatology of sex steroid deficiency and its relief by appropriate hormone replacement, but also in the effects on structure and function of the entire uro-genital tract. Changes in the epithelium of the aging male urethra were first described over

Table 3 Adverse reactions to testosterone 1963–2002 (Yellow Card) UK medicines control agency

Cutaneous + local reaction	117	Implant + injection complications 90, rash 15
Psychiatric + general	27	Aggression 6,depression 3 (suicide 1)
Endocrine + metabolic + musculo-skeletal	17	Muscle cramps 3, arthralgia 3, hirsutism 1, diabetes 1
Gastrointestinal + liver + respiratory	16	Diarrhea 7, nausea 3, abdominal pain 3, jaundice 2
Vascular	15	Cardiac 8, CVA2, DVT 4, embolus 1
Neurological + eye	13	Paraesthesia 6, headache 6(OD-CVA1)
Neoplasms + urological	9	Prostate 2, (sarcoma 1), breast 1, priapism 2, testicular pain 2, renal failure 1

CVA2 = Cardiovascular 2; DVT4 = Deep Vein Thrombosis 4; and OD-CVA1 = Headaches 6, Cerebrovascular Accident 1

60 years ago and compared with the karyopyknotic index in vaginal smears as a "simple test for hormone deficiency in the male" [44].

It is now recognized that underlying the ED in testosterone deficiency are metabolic and structural imbalances in the corpus cavernosum, and these may contribute to venous leakage reversible by TRT [45]. Fortunately, as with the reduction in muscle mass and accumulation of visceral fat seen in diabetes and metabolic syndrome, these changes are reversible by androgen treatment, with a consequent improvement in erectile function [46–48].

Although a high proportion of the men seen in this study had ED (83%), especially associated with loss of morning erections, this was not primarily a study of sexual dysfunction. No correlation was seen with erectile function and TT or PSA prior to treatment [49], and there is evidence that ED does not predispose this population to PCa [50].

ED risk factors are common among patients with LUTS, with several studies indicating a significant association, both in prevalence and severity [51]. The metabolic syndrome is associated with an overactivity of the autonomic nervous system, as well as with markers of inflammation, such as C-reactive protein (CRP), that might underlie other inflammatory conditions such as chronic prostatitis. Along with improvement of the metabolic syndrome, reduction of the International Prostate Symptom Score (IPSS) (symptom score for LUTS), postvoid bladder volume, and CRP have also been reported with testosterone treatment [52]. Another study showed that TT, biotestosterone (BT), and dihydroepiandrosterone sulphate (DHEAS) levels were strongly inversely related to the IPSS, while SHBG values and the IPSS were strongly positively correlated. Adjusting for age reduced these associations, but BT and DHEAS levels still had negative relationships with the IPSS, and SHBG remained positively related to LUTS [53]. Urogenital smooth muscle relaxation is mediated by nitric oxide, which is also increased by TRT, and phosphodiesterase type 5 inhibitors used for treatment of ED appear to also have a beneficial effect on LUTS [54,55].

These studies indicate the importance of testosterone in maintaining both lower urinary tract and genital function in men and that testosterone deficiency may contribute to more aggressive phenotypes of PCa. The UKAS study reported here indicates that in men treated for androgen deficiency, TRT is safe when carefully monitored.

Conclusions

These converging lines of evidence all point to any putative link between TRT and the induction of PCa being indeed a myth. Given suitable screening with PSA, DRE, and similar monitoring during treatment, TRT appears safe in relation to the development of PCa in the aging male population. It is important that patients and physicians understand that a small proportion of patients will develop clinically significant malignancy, as with aging. The majority of treated men however will have no adverse effect on the prostate but rather many positive benefits on physical and psychological well-being, erectile function, and the factors underlying LUTS. Physicians and surgeons considering the many potential benefits of TRT for their patients should not be deterred from giving it by theoretical fears, where careful and regular safety monitoring is in place.

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