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Testosterone Substitution and the Prostate

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Abstract

Testosterone substitution is reported to produce a wide range of benefits for men with hypogonadism that include improvements in muscle mass, body composition, mood, bone density, libido, and cognition. Understanding the actions of exogenous testosterone on the prostate gland is important since testosterone is the major regulator of growth and function of this organ. To date, clinical studies of the effects of testosterone substitution on prostate health suggest that testosterone substitution does not exacerbate lower urinary tract symptoms (LUTS) attributable to benign prostatic hyperplasia (BPH), although it may increase prostate volume. The greatest concern associated with testosterone substitution is the possibility of increased risk of prostate cancer. The relationship between prostate cancer and testosterone is not completely understood. While there is currently no compelling evidence that the use of testosterone substitution in men with hypogonadism increases the risk of prostate cancer, close monitoring of the levels of testosterone and prostate-specific antigen (PSA) along with regular digital rectal examination (DRE) are advised to detect early signs of prostate cancer in subjects receiving long-term testosterone substitution. This review considers the physiological and pharmacological actions of testosterone on the prostate gland, and the risks of BPH and prostate cancer in ageing males receiving testosterone substitution for the treatment of hypogonadism.

Keywords: Benign prostatic hyperplasia; Hypogonadism; Lower urinary tract symptoms; Prostate; Prostate cancer; Prostate-specific antigen; Testosterone substitution; Testosterone therapy

1. Introduction

Testosterone substitution is increasingly considered as a therapeutic option that confers a number of clinical benefits in men with hypogonadism [1,2]. The growing awareness that some aspects of age-related endocrine disorders in older men, and in particular androgen deficiency, may be managed through testosterone substitution has prompted a resurgence of interest in the physiological and pathophysiological role of testosterone, particularly in regard to prostate function and health.

There is considerable interest in assessing and studying the potential risks of testosterone substitution alongside clinical appraisal of the benefits of this therapy in male subjects [3–6]. The prostate is a particular focus in this regard, since this organ is known to be closely controlled and influenced by androgens and sex hormones. Furthermore, two clinical conditions affecting and involving the prostate – benign prostatic hyperplasia (BPH) and prostate cancer – occur commonly in ageing males, the same population affected by conditions such as late-onset hypogonadism (LOH) and in whom testosterone substitution may be considered as a therapeutic option.

An understanding of the effects of testosterone on the prostate helps inform optimal clinical use and defines the parameters for monitoring and control of testosterone substitution in male patients. This article considers the role of testosterone in prostate growth and function and reviews the current and emerging evidence regarding the impact of testosterone and testosterone substitution both on the development of BPH and associated lower urinary tract symptoms (LUTS) and on the development and progression of prostate cancer.

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2. Androgens and the prostate

The specific function of the prostate gland remains unknown, although it is believed that this organ is important in protecting the lower urinary tract from infection and inflammation, and for male fertility [7]. Huggins and Hodges demonstrated in 1941 that prostatic cancers are androgen-dependent by showing that the deprivation of testosterone slowed the progression of prostate cancer [8]. Attempts to understand the physiology of the prostate are viewed as important since this organ is the most common site of neoplastic transformation in men, with prostate cancer affecting an estimated 1 in 6 males in the western world [9]. The prostate is also the most common site of benign neoplastic disease, with more than 50% of men aged >50 years thought to have BPH [10].

Human prostatic epithelial cells synthesize and secrete a number of unique proteins into ejaculate, including prostate-specific antigen (PSA). The highly specific nature of these proteins means that detection of abnormal levels of PSA is useful in the diagnosis and monitoring of neoplastic malignancies of prostate tissue. This marker is also valuable in assessing the response to surgical and therapeutic management of prostatic cancer and its metastases [7].

Endogenous testosterone is known to be the major growth and functional regulator of the prostate and is essential to the development and maintenance of this organ throughout life. Prostate development, differentiation, and maintenance are known to be closely linked to the bioavailability of testosterone and other related sex hormones. Between the ages 10–20 years when serum testosterone levels rise dramatically in males, there is pronounced, exponential growth of the prostate controlled by the balanced agonist and antagonist abilities of androgens to stimulate cell proliferation on the one hand and to inhibit the rate of cell death in prostate tissue on the other. After the age of 20 years, and under the continuing presence of testosterone, the healthy prostate achieves a steady state of self-renewal and maintenance [7].

Within the prostate, testosterone is enzymatically converted to an active metabolite, 5α-dihydrotestosterone (DHT), by 5α-reductase. Once formed, DHT can bind reversibly to the androgen receptor to regulate prostatic cellular proliferation and survival, or may be further metabolized along a number of alternative pathways (Fig. 1) including that which yields the endogenous oestrogen 3β-diol. 3β-diol, in contrast to DHT, has inhibitory effects (mediated via oestrogen receptors) on cell proliferation. It is thought that normally the prostatic level of DHT remains constant even during diurnal and episodic variations in the serum levels of both free and total testosterone [7].

The presence of DHT and its binding to androgen receptors can directly up-regulate expression of prostate-specific differentiation markers such as PSA, and locally active growth factors – the andromedins. These andromedins stimulate the proliferation of so-called transit amplifying (TA) cells within the prostate and allow the survival of these TA cells, and of intermediate and secretory luminal cells, within prostate tissue. It is speculated that testosterone and DHT may play a permissive or an inductive role in neoplastic diseases of the prostate, and that DHT may hold a key to

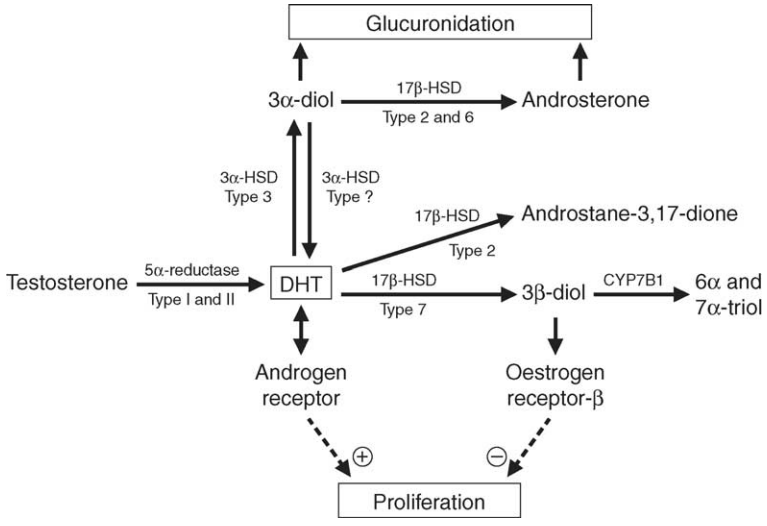

Fig. 1. The enzymatic pathways of testosterone metabolism within the prostate. Reproduced with permission [7]. Copyright© 2004 Cambridge University Press.

understanding how to control and manage some of the neoplastic changes associated with prostatic disease [4,5,7].

3. Benign prostatic hyperplasia – the role of androgens

It has been recognized for many years that the development of BPH requires the presence of androgens. Epidemiological studies have shown that testosterone levels decrease exponentially with age, while DHT levels remain relatively constant, and in BPH are slightly elevated [11]. Two clinical observations confirm such a relationship. First, the use of a 5α-reductase inhibitor has a significant effect on prostate size and indirectly alleviates LUTS caused by BPH [12]. Second, hypogonadal men treated with testosterone substitution did not demonstrate a significant increase in BPH incidence compared with eugonadal men [13].

However, despite the clear importance of androgenic steroids, particularly testosterone and DHT, in prostate growth, the pathogenesis of BPH has not been fully elucidated. While hypogonadism (defined in this study as serum total testosterone level <300 ng/dL or <10.4 nmol/L) has been observed in approximately 20% of elderly men with LUTS, prostate volume did not correlate with serum testosterone levels [14]. The oestradiol:testosterone ratio has, however, been implicated in the pathogenesis of BPH [14,15]. Oestradiol levels have been found to be lower in men with prostate cancer compared with age-matched men with LUTS [15].

The symptoms of BPH typically reflect progressive growth and change in the prostate gland. As the gland enlarges, it begins to obstruct the urethra, causing urinary difficulties: LUTS. LUTS is the most common symptom of BPH and includes hesitant, interrupted weak stream; urgency and leaking or dribbling; and more frequent micturition, especially at night. An enlarged prostate (benign prostatic enlargement [BPE]) is evident in around 50% of patients with histological evidence of BPH [15], but LUTS suggestive of BPH can be present without prostate enlargement.

3.1. The pathophysiology of BPH

In BPH, there is an increase in the cellular content of the transition zone of the prostate. This growth may be the result of an enhanced number of epithelial stem cell units, or enhanced proliferation by TA cells before they mature to non-proliferating luminal secretory cells, or a decreased ability of androgen receptor to limit the proliferation of luminal secretory cells. The condition is also associated with an increase in the number of stromal cells and enhanced andromedin production from these cells [7].

In theory, in order to inhibit the effects of excessive andromedin production, treatment of BPH could involve androgen ablation. In practice, however, this is too drastic a measure, since systemic androgen ablation is associated with unacceptable side-effects such as loss of libido and detrimental effects on bone density and muscle mass [7]. Instead, the selective inhibition of 5α-reductase – causing a reduction in prostatic DHT levels – has been shown to be an effective form of targeted treatment for BPH [4,5,12]. Clinical studies of long-term use of finasteride at a dose of 5 mg/day for the clinical management of BPH found that treatment caused a significant decrease in total urinary symptom scores, increasing maximal urinary flow rates and significantly reducing prostatic volume over 1 year compared with placebo [12,16]. Treatment of BPH with agents such as finasteride and dutasteride, which selectively inhibit 5α-reductase, has been shown to reduce DHT levels without affecting circulating testosterone levels. In this way, these treatments target the prostate and manage the aberrations in local DHT production, while having minimal systemic side-effects.

4. Testosterone substitution

4.1. Testosterone substitution and BPH

Since androgens are important to the pathophysiology of BPH, it might be thought that males with hypogonadism would be less likely to develop BPH and that the use of testosterone substitution could promote a tendency towards BPH. However, in practice, the relationship between circulating androgen levels and BPH is less clear-cut. Hypogonadism does not preclude the development of BPH. Indeed, an epidemiological study of elderly men demonstrated that around one-fifth of subjects with evident LUTS are also clinically hypogonadal [15].

Close attention has also been paid to the potential for testosterone substitution to induce prostate growth and enlargement and to precipitate BPH. Although early studies appeared to support the view that therapeutic use of testosterone substitution was associated with modest increases in prostate volume, the observed slight increases in both prostate size and in the levels of PSA seen during treatment nevertheless remain within normal limits [4]. Indeed, more recent evidence from placebo-controlled clinical studies of testosterone substitution in hypogonadal men suggest that the dif-

ferences between placebo- and testosterone-treated subjects in terms of prostate volume, PSA, and symptoms of LUTS are clinically insignificant [3–5,13]. Testosterone substitution has been shown to increases prostate volume to the same extent as in age-matched controls, to restore low PSA levels to normal in testosterone-deficient men, and to increase PSA levels which remain in the normal range [6,17,18].

A controlled cross-sectional study comparing prostate volumes of men with newly diagnosed hypogonadism before treatment, with those of controls and of men with hypogonadism managed for at least 6 months with testosterone substitution, suggests that exogenous testosterone has no adverse effects on prostate growth [13]. The study ($n = 200$) noted that subjects with untreated hypogonadism had significantly lower prostate volume (12.2 mL) than controls (22.9 mL) or testosterone-treated men (21.3 mL). It was also found that hypogonadal men had serum PSA levels of 0.64 μg/mL compared with 0.98 μg/mL in testosterone-treated hypogonadal men and 1.02 μg/mL in normal controls. Thus treatment of hypogonadism with testosterone substitution, given by a variety of routes, was seen to elevate PSA levels and increase prostate volume, but the end result was that levels were normalized to values typically seen in otherwise healthy, normal controls. This study also found that there were no differences in uroflow parameters (urine volume and flow rates) between any of the 3 study groups, suggesting that testosterone substitution did not induce LUTS [13].

Another study that supports the good tolerability of testosterone substitution with respect to BPH and PSA involved the retrospective follow-up of hypogonadal men receiving testosterone for a period of 2 years [19]. In this study, hypogonadal males (bioavailable serum testosterone levels $\leq$72 ng/dL) receiving intramuscular testosterone every 2 weeks for 2 years were closely assessed at regular intervals by means of laboratory and clinical assessments. The findings in these subjects were compared to those for a group of control (untreated) hypogonadal men. This study found that there was no significant rise in PSA levels between treated and untreated patients and that there was no significant difference between the rate of BPH in control and treated subjects [19].

Current opinion and recommendations regarding the use of testosterone substitution in men with hypogonadism is that there is no evidence that this treatment will lead to BPH; however, men with hypogonadism given testosterone substitution may occasionally suffer from LUTS [1,2,6,20,21]. Routine measurement of serum PSA is not advised or recommended in young hypogonadal men starting testosterone substitution [6]. Testosterone substitution is, however, contraindicated in men with severe bladder obstruction and an enlarged prostate and is partially contraindicated in cases of moderate LUTS. Once the LUTS is treated, testosterone substitution may be started [1].

4.2. Testosterone substitution and prostate cancer

Whether testosterone promotes the development of prostate cancer remains to be fully elucidated. There are concerns that long-term administration of testosterone to older men could unmask microscopic foci of prostate cancer, but there is currently insufficient evidence to state that testosterone substitution has a causative role in prostate cancer [1–3,6,20]. It is clear, however, that the proliferative effects of testosterone on prostate tissue growth are an absolute contraindication to use of testosterone substitution in any subject suspected of having carcinoma of the prostate gland [1–3].

Current understanding of the pathogenesis of prostate carcinogenesis is that chronic and acute inflammation, in conjunction with dietary and other environmental factors, targets prostate epithelial cells for injury and destruction. As a regenerative response to such insults, there is increased cell proliferation, which may increase the genetic instability of these cells, driving further genetic damage and producing invasive cancer [7]. Even with such changes, oncogenic pathways appear to remain dependent on the binding of androgen to its receptors in the nuclei of neoplastic cells, which may partly explain the evidence for a permissive role of androgens in prostate cancer progression and development.

Nevertheless, the precise relationships between androgens and the development of prostate cancer continue to be the subject of intense research study and debate. It is known from animal studies that hypertestosterone states promote prostatic cancer; conversely, for a number of years it has been clear that in humans, surgical or medical castration effects a dramatic regression of prostate cancer growth and development, suggesting a ‘‘permissive’’ role for androgens in prostate cancer growth [4].

More controversial, however, is the relationship between serum androgen levels and prostate cancer. The study of endocrine patterns in patients with newly diagnosed prostate cancer suggests that there is no close correlation between serum testosterone and a patient’s serum PSA levels or the clinical and pathological stage of prostate cancer [14]. Furthermore, conflicting reports exist regarding the associations between levels of serum testosterone and the incidence of prostate cancer: several studies have found a positive association, while others have found a negative or no

association. The preponderance of evidence does not support the concept that normal serum testosterone levels are associated with an increased risk of prostate malignancy [4].

This issue of what constitutes a ''dangerous'' serum testosterone level with respect to prostate cancer risk is further confused by the observation that low pre-treatment testosterone levels in patients who go on to develop prostate cancer have been associated with more aggressive disease, a worse prognosis, and a poorer response to treatment [22–26].

For example, a study in 144 patients with stage D_2 prostate cancer found a significant correlation between low pre-treatment serum testosterone levels and poor response to treatment ($p = 0.0304$) and shorter overall survival ($p = 0.003$), suggesting that low testosterone at the time of diagnosis is indeed associated with a poorer clinical outcome than normal testosterone levels [25]. Similarly, retrospective chart analyses of data from patients with prostate cancer involving bony metastases suggest that low testosterone is a poor prognostic factor in patients undergoing androgen ablation therapy irrespective of their tumour grade [24]. Thus, low levels of testosterone pre-treatment seem to indicate aggressive, high-grade tumours in men with newly diagnosed prostate cancer.

When prostate cancer is more localized, total testosterone levels predict pathological stage, and are not correlated with clinico-pathological features of disease such as PSA, clinical stage, or Gleason score [22]. High testosterone levels are associated with higher rates of metastatic relapse, and low pre-treatment free and total testosterone levels seem to predict more aggressive disease and metastases [22,23].

It has been suggested that a low serum testosterone level could be viewed a potential marker of occult prostate cancer. In a study of 77 men with low total or low free testosterone levels, who had normal PSA levels ($\leq$4.0 ng/mL) and normal findings on digital rectal examination (DRE), it was shown that 14% of the entire group and 29% of those aged $\geq$60 years had a prostate cancer demonstrable histologically (Gleason scores of 6 or 7) [27].

As to the question of whether use of testosterone substitution promotes or encourages the development or progression of prostate cancer, prospective studies have shown a low frequency of prostatic malignancies during long-term treatment with testosterone [3,17,18]. In a recent review article considering all available evidence on testosterone substitution and its safety, Rhoden and Morgentaler [3] note that from a reported 461 men who had received testosterone substitution for 3 to 36 months in controlled studies, only 5 cases of prostatic cancer (1.1%) were detected, suggesting a prevalence rate for this cancer that is similar to that seen in the general population of ageing males (Table 1) [17–19,28–33].

In a study of 75 men with hypogonadism who were treated with testosterone substitution for 12 months, there was no increase in the rate of prostate cancer among men receiving therapy, and no change in the serum levels of PSA, even among men with a history of prostatic intraepithelial neoplasia [34]. This finding suggests that testosterone substitution should not be contraindicated even in patients with a condition which is often viewed as precancerous in its characteristics.

Other clinical studies of testosterone substitution in hypogonadal men suggest that treatment may be asso-

Table 1
Studies of testosterone substitution and the reported on-treatment incidence of prostate cancer

Study (year) [ref. no.]	Duration (months)	Increase in PSA[a]		Prostate cancer		Method of administration
		Placebo[b]	Testosterone[b]	Placebo[b]	Testosterone[b]	
Hajjar et al. (1997) [19]	24	–	–	0/27	0/45	Intramuscular
Sih et al. (1997) [28]	12	0/15	0/17	0/15	0/17	Intramuscular
Dobs et al. (1999) [29]	24	–	1/33	–	2/33	Intramuscular
		–	0/33	–	1/33	Nonscrotal patch
Snyder et al. (1999) [30]	36	7/54	13/54	0/54	1/54	Nonscrotal patch
Snyder et al. (2000) [31]	36	–	–	–	0/18	Scrotal patch
Wang et al. (2000) [32]	6	–	0/76	–	0/76	Nonscrotal patch
		–	1/73	–	0/73	Transdermal 50 mg
		–	4/78	–	1/78	Transdermal 100 mg
Kenny et al. (2001) [33]	12	3/33	8/34	0/33	0/34	Nonscrotal patch
Wang et al. (2004) [18]	42	–	7/163	–	3/163	Topical gel
Dean et al. (2004) [17]	12	–	21/371	–	3/371	Topical gel

 PSA = prostate-specific antigen.
[a] Increase in PSA was defined as any increase to a level >4 ng/mL, except in Snyder et al. [30], where it was defined as an increase of >1.5 ng/mL per year or an increase of 2 ng/mL between any two measurements; and in Wang et al. [18], where it was defined as any increase to a level >5.5 ng/dL.
[b] Number/total number.

ciated with rises in serum PSA levels [17,18,35]. For example, in one study of 54 subjects, the mean pre-treatment PSA level was 1.86 ng/mL. This increased to 2.82 ng/mL after a mean 30.2 months on treatment ($p < 0.01$) [35]. In a long-term study of 163 men receiving testosterone gel for up to 42 months, PSA levels rose from a baseline of 0.85 ± 0.06 ng/mL to 1.11 ± 0.08 ng/mL following treatment ($p < 0.001$) [18]. In a long-term study of another testosterone gel, mean PSA was 1.26 ± 0.05 ng/mL at baseline, and increased by 0.45 ng/mL at 12 months ($p < 0.001$) [17]. While these rises in PSA were statistically significant, such increases in serum PSA remained within the normal range for PSA.

As with all clinical studies, published testosterone substitution studies that assess prostate cancer risk do have their limitations. These include: small sample sizes, selection bias, short follow-up period (while prostate cancer is a slow-growing tumour), mainly epidemiological observations with historical correlations on risk, no randomization – mean testosterone levels before and after testosterone substitution are borderline (this increases the possibility that many patients were eugonadal rather than hypogonadal; and the effect of testosterone substitution on prostate cancer risk is still not known in eugonadal men), and a lack of basic research to back up the claim. It is clear that data from large-scale, longer-term studies would be needed before definitive conclusions about prostate cancer risk due to testosterone substitution could be drawn.

5. Monitoring and measurements of the prostate during testosterone substitution

The current opinion is that before beginning testosterone substitution in older men with hypogonadism, it is prudent to exclude the presence of prostate cancer.

Despite continuing controversy over the pathological role of testosterone in prostate cancer pathology (and a lack of long-term studies), current opinion and advice regarding the use of testosterone substitution in hypogonadal men is clear. In subjects presenting with hypogonadism and a known diagnosis or suspicion of prostate cancer, treatment with testosterone substitution is contraindicated.

In all men aged $\geq$40 years who are to be considered for testosterone substitution, it is recommended that baseline measurements and clinical assessments are made to exclude the possibility of prostatic malignancy (Table 2) [1–3]. In particular, DRE and determination of serum PSA levels should be viewed as mandatory pre-treatment tests, and should be repeated at quarterly intervals during the first year on therapy and annually thereafter during the course of testosterone substitution. In this way, through ongoing monitoring of prostatic health, it should be possible to ensure early diagnosis of any pre-existing or unmasked cancers that might be susceptible to exogenous testosterone treatment [1,3]. Development of palpable nodules, asymmetry, or appearance of areas of increased firmness on DRE warrant further investigation by biopsy, and sudden rises in PSA or increases to >4.0 ng/mL in serum PSA should also prompt further examination and tests for cancer [3,36]. In addition, every 3 months in the first year of treatment, and then once or twice a year, serum testosterone levels and haematocrit and haemoglobin should be assessed.

With close monitoring for evidence of urinary symptoms every 6 to 12 months during testosterone substitution in all older men receiving treatment, any emergent cases of LUTS or BPH can be detected and managed [2]. The management of men with coex-

Table 2
Recommendations for patient monitoring during testosterone substitution

Time	Recommended steps
Baseline	Determine baseline voiding history or use standardized questionnaire Determine history of sleep apnoea Perform DRE Perform blood tests for baseline testosterone levels, PSA, and haematocrit or haemoglobin Perform prostate biopsy if PSA level is >4.0 ng/mL or DRE is abnormal
Follow-up	Perform efficacy evaluation with dosage adjustment for suboptimal response at 1–2 months Perform monitoring evaluation with repeated testing every 3–6 months for the first year and annually thereafter Assess urinary symptoms and presence or exacerbation of sleep apnoea or gynaecomastia Perform DRE Perform blood tests for testosterone, haematocrit or haemoglobin, and PSA Perform prostate biopsy if DRE shows change or there is a substantial increase in PSA

Reproduced with permission [3]. Copyright© 2004 Massachusetts Medical Society. All rights reserved. DRE = digital rectal examination. PSA = prostate-specific antigen.

istent BPH and hypogonadism using a combination of agents such as finasteride plus testosterone substitution is also possible through programmes that ensure careful patient monitoring and assessment over the course of chronic treatment of these conditions [2].

6. Conclusions

The prostate gland is highly sensitive to androgens, which determine growth and proliferation of cells and tissue in this poorly understood organ. As growing numbers of ageing males receive testosterone substitution for management of the signs and symptoms of hypogonadism, there has been a renewed interest in the role of testosterone in prostate health and greater attention paid to the safety profile of testosterone substitution in terms of BPH and prostate cancer. Current evidence suggests that treatment with testosterone does not worsen LUTS attributable to BPH. Clinicians should nonetheless be alert to development of symptoms of BPH during testosterone substitution. The use of testosterone substitution is contraindicated in cases of known prostate cancer due to the permissive role of testosterone in malignancies of the prostate gland, but there is no good evidence to date to suggest that long-term use of testosterone in hypogonadal men promotes or induces prostatic cancer per se. Current guidance is that pre-treatment assessments to exclude malignancy plus careful monitoring during the use of testosterone substitution should allow early detection of any treatment-related effects on prostatic cell proliferation that might be detrimental to patient health.

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