The Aging Male 2003;6:166–174

Review

The effect of androgen supplementation therapy on the prostate

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Key words: TESTOSTERONE, PROSTATE CANCER, PROSTATIC HYPERTROPHY

ABSTRACT

With the recent availability of transdermal formulations, androgen supplementation therapy is increasingly being prescribed for men in their 50s and 60s. With the growing use of testosterone products, there is concern about the long-term risks of androgen supplementation therapy, particularly on the prostate. This article reviews what is known about the safety of testosterone replacement therapy in terms of the potential risks for development of symptomatic benign prostatic hypertrophy (BPH) and prostate cancer. Androgens are undoubtedly involved in the growth of benign prostatic nodules, as a permissive factor in the etiology of prostate carcinoma and in the enhancement of the growth of active prostate cancer. Their role in the initiation of either disease is less clear. Available data support the safety of such treatment in the short term. Caution is still advised in the interpretation of these findings, as the studies producing the data have involved relatively small numbers of participants. Until large, long-term, placebo-controlled studies have been conducted and analyzed, questions about the long-term safety of testosterone supplementation therapy in older men will remain.

INTRODUCTION

In the USA, change in lifespan is altering population demographics, resulting in a growing number of men in their sixth decade of life and beyond. These aging men have every expectation that medical science will preserve their vitality and sexual health well into their retirement years. As a result, there is growing interest in the effect of aging on serum testosterone concentrations. It has been demonstrated in cross-sectional studies[1–3], and confirmed in longitudinal studies[4–9], that serum testosterone levels decline with age. Consequently, a substantial proportion of older men exhibit serum total testosterone levels below the range for younger men. In healthy older men, serum testosterone levels are usually mildly decreased and may be associated with symptoms such as erectile dysfunction, loss of libido and muscle weakness[10,11].

With the recent availability of transdermal formulations, testosterone supplementation therapy is becoming more popular. It is now possible to restore serum testosterone levels to the eugonadal range[12], without the inconvenience of twice-monthly injections of depot-testosterone preparations[13] or the inconsistently bioavailable oral androgen preparations[14] (with the exception of oral testosterone undecanoate, which is not available in the USA). According to pharmaceutical industry estimates, testosterone prescriptions have risen almost 30% between 2001 and 2002[15].

With many men in their 50s and 60s being prescribed testosterone products, there is a concern

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about the long-term risks of testosterone replacement therapy, particularly its effects on the prostate. Thus, it is appropriate to review what is known about the safety of testosterone replacement therapy in terms of the potential risks for development of symptomatic benign prostatic hypertrophy (BPH) and prostate cancer.

CELLULAR MECHANISMS OF PROSTATE CELL GROWTH

The normal prostate is small, weighing about 30 g, and is nearly the same size and shape as a walnut. The prostate is made up of several different tissues including smooth muscle, fibroblasts and a variety of epithelial cells. Dihydrotestosterone (DHT) is the androgen which has the greatest mitogenic effect on the prostate. DHT results from the enzymatic metabolism of testosterone by 5α-reductase within androgen target cells (skin, liver, prostate and other organs) that contain the enzyme[16]. Testosterone is also metabolized to estradiol by the aromatase enzyme complex in brain, fat and the testes[16]. In typical healthy males, the ratios of the resulting serum levels of DHT and estradiol to the total testosterone level are approximately 1 : 10 and 1 : 200, respectively.

Glandular epithelial cells and a subset of endothelial cells are androgen dependent; without sufficient levels of circulating androgen, their rate of cell proliferation is lower than their rate of cell death[17,18]. The mitogenic effect of androgen on the prostate is not direct, but rather androgen acts on stromal cell androgen receptors to induce synthesis and secretion of growth factors that, in turn, regulate the growth and differentiation of epithelial cells. Numerous growth factors such as epidermal growth factor[19], transforming growth factor-α[20], transforming growth factor-β[21,22], insulin-like growth factors[23,24], fibroblast growth factors[24,25], nerve growth factor[26], vascular endothelial growth factor[27] and interleukins[28] are involved in prostate cell growth, development and death[29].

Changes in hormone levels, mutations in androgen receptors, changes in growth factor synthesis and mutations in growth factor receptors have all been identified in prostate cancer[30–34]. However, there is no indication which, if any, of these events triggers malignancy. Androgens are required for the growth, maintenance and functional activity of prostate cells and, undoubtedly, they play a permissive role in prostate carcinogenesis. However, the initiation, development and progression of microscopic to clinically important prostate cancer are probably the result of multiple factors that include genetic alterations as well as dietary and other environmental agents[35,36].

EPIDEMIOLOGICAL DATA

Males castrated before puberty and those with androgen insensitivity syndromes do not develop BPH or prostate cancer[37,38], so it is clear that androgens must be present at some point in life for these diseases to develop. Clues to understanding the relationship between serum testosterone levels and prostate cancer have been sought in epidemiological studies. Conflicting data on the relationship are provided by population studies. Shaneyfelt and co-workers[39] performed a meta-analysis of five published epidemiological studies on hormonal predictors of risk for prostate cancer. They concluded that men with serum testosterone levels in the upper quartile of the population distribution have an approximately two-fold higher risk for developing prostate cancer than patients in the lowest quartile. On the other hand, Eaton and associates[40] reviewed the data from eight prospective epidemiological studies (including all five studies analyzed by Shaneyfelt) and found no large differences in circulating androgens between men who later develop prostate cancer and those who do not. Likewise, Slater and Oliver[41] felt that the link between testosterone levels and the development of prostate cancer is weak. They reasoned that the weakness of the overall effect of testosterone can be explained in two possible ways. 'One explanation is that testosterone plays no apparent direct role in the development of prostate cancer. Alternatively, testosterone influence may be modified by other circumstances, such as different genetic predispositions, diets and infectious damage impacting at different stages of cancer development.' Considering the number of genes known to affect androgen metabolism, the latter explanation seems more probable.

Additional observations support the view that the prostate cancer risks from use of testosterone hormone replacement may not be as great as feared. In fact, the opposite may be the case. Some investigators have found that low levels of pretreatment serum total testosterone consistently

predict more aggressive disease, worse prognosis and non-responsiveness to hormones in patients with metastatic prostate cancer. Specifically, low serum testosterone in men with newly diagnosed prostate cancer is associated with higher tumor microvessel and androgen receptor density as well as with higher Gleason score[34] and an increased likelihood of non-organ-confined disease[42].

REVIEW OF CLINICAL TRIAL DATA

Without a solid understanding of the physiology and pathophysiology of BPH and prostate oncogenesis it can be difficult to interpret the results of clinical trials. Moreover, the majority of well-designed studies of testosterone replacement therapy have enrolled predominantly hypogonadal young males. The studies of testosterone treatments for aging men have generally been small and of short duration and have excluded men with elevated prostate specific antigen (PSA), prostate symptoms and abnormal uroflow. Mindful of these caveats, clinicians can, nevertheless, find useful information concerning the clinical safety of androgen therapy in a review of the literature.

Benign prostatic hypertrophy

Precipitation of BPH in patients receiving testosterone supplementation is an uncommon occurrence based on published series. Marin[43] treated 31 middle-aged men (mean age 57.7 ± 21 years) in a double-blind fashion with transdermal testosterone, transdermal DHT, or placebo during 9 months. There were no detectable changes in prostate volume (measured by ultrasound), PSA concentration, genitourinary history or urinary flow measurements in any of the groups.

In a multicenter, open-label study of 29 hypogonadal men (mean age 39.5 ± 13.6 years) who received testosterone enanthate injections, followed by 8 weeks of androgen withdrawal, followed by 1 year of non-scrotal transdermal testosterone therapy, Meikle and colleagues[44] showed that mean prostate volume (measured by transrectal ultrasonography) decreased significantly during the androgen withdrawal period, then increased significantly during the transdermal testosterone treatment period, going from 14 g (range 7–33) to 18 g (9–32), $p < 0.001$. The maximum prostate size was reached at 3 months and was comparable to that measured during testosterone enanthate therapy. No patient developed symptomatic BPH. PSA levels significantly decreased from the testosterone enanthate period during the androgen withdrawal period, and then significantly increased during the transdermal testosterone treatment period (mean increase of 0.66 ng/ml, $p < 0.001$). Despite the increase in PSA concentration, the mean level was still within normal limits and well below the values observed during the period when the men were receiving testosterone enanthate injections.

Snyder and associates[45] treated 18 hypogonadal men with testosterone for 3 years and noted that prostate volume increased to normal over the initial 6 months, with no appreciable increase in prostate size after 6 months. Canale and coworkers[46] treated six patients affected by idiopathic hypogonadotropic hypogonadism with pulsatile gonadotropin releasing hormone, and noted a significant increase in prostate volume at 3 and 6 months (by 70.3% and 97.7%, respectively).

In a controlled, cross-sectional, aged-matched study of 78 testosterone-treated (at least 6 months) hypogonadal men, 47 newly diagnosed hypogonadal men before testosterone treatment and 75 normal men, Behre and associates[47] measured prostate volume (by transrectal ultrasonography), PSA and sex hormone levels, and uroflow parameters. Eugonadal testosterone levels were achieved with testosterone treatment, and testosterone treatment resulted in prostate volume and PSA levels comparable with normal men. No differences in uroflow parameters were detected between the three groups. Only 12 of the 47 men were older than 40 years.

Hajjar and colleagues[48] conducted a retrospective assessment of 45 elderly hypogonadal men (mean age 71.8 ± 1.7 years) receiving testosterone replacement therapy (by injection) and 27 elderly hypogonadal men who chose not to receive testosterone. At 2 years ($n = 26$ and 15 for the treatment and control groups, respectively) there was no statistically significant difference in the change in serum PSA levels. The control group had a higher, but statistically insignificant, rate of BPH than the treated group (assessed by digital rectal examination and subjective evaluation using the International Prostate Symptom Score (IPSS)).

In a randomized cross-over trial of testosterone enanthate and placebo injections for 3 months each in 13 hypogonadal men aged 57–76 years, Tenover[49] demonstrated a sustained increase in PSA levels with testosterone enanthate treatment but no increase in prostate volume. Holmang and co-workers[50] administered testosterone undecanoate (an oral preparation) or placebo daily for 8 months to 23 middle-aged eugonadal men (aged 40–65 years) with urinary tract symptoms. There was no change in serum PSA over the course of the study, and mean prostate volume increased by 12% in the treated group. There were no changes in micturition habits or urine flow. Sih and associates[51] studied the long-term effects of testosterone administration in older hypogonadal men. Fifteen men (mean age 68 ± 6 years) were randomly assigned to receive placebo and 17 men (65 ± 7 years) received testosterone, and after the 1-year treatment period there were no significant changes in serum PSA levels between the two groups. Gooren[52] followed 33 hypogonadal men treated with oral testosterone undecanoate for a minimum of 10 years. Eight men were older than 50 years at the start of the study. Over the 10-year period, in two of the six, a mild reduction in urine flow was observed. No other clinically important events were seen in this small cohort. Digital examination of the prostate did not reveal signs of prostate tumors.

In a multicenter, randomized, parallel study comparing 6 months of treatment with one of two dosage forms of a testosterone gel (50 or 100 mg) or a testosterone patch (5 mg) in 227 hypogonadal men (more than half the subjects in each group were over 50 years of age), Wang and colleagues[12] reported that the increase in mean serum PSA was correlated with serum levels of testosterone. The greatest increase in serum PSA was in the 100 mg testosterone gel group at 3 months (mean increase was 0.30 ng/ml). The serum PSA rose with treatment, but stabilized with continued administration and plateaued after 3 months, and it was not associated with an increase in prostate symptom score (IPSS) or a decrease in urine flow rate. In five of the 227 patients, the serum PSA rose above 4 ng/ml. Most of these patients had enlarged prostates suggestive of BPH. One patient was found to have prostate cancer upon biopsy of the prostate.

Kaufman and associates[53], reporting on the 30-month follow-up data for the extension period, noted that collectively the serum PSA statistically significantly increased from a mean of 0.87 ng/ml to 1.02 ng/ml, and that mean total IPSS improved from baseline to final visit. In an analysis of a subset of the 52 geriatric patients (mean age 63 years) enrolled in this trial, Kaufman[54] found that mean serum PSA levels were increased at 6 months from the baseline measurement by 0.3, 0.6 and 0.1 ng/ml for the testosterone gel 50 mg, testosterone gel 100 mg and testosterone patch 5 mg groups, respectively, although these differences were not statistically significant.

Prostate cancer

Prostate cancer is the most prominent of the safety concerns associated with testosterone treatment in older men. There is no evidence that normal levels of testosterone promote the development of cancer of the prostate, but it is clear that the administration of testosterone enhances a pre-existing prostatic malignancy. In a study that investigated whether the effectiveness of chemotherapeutic agents would be enhanced by concurrent testosterone therapy, Fowler and Whitmore[55] found that among 52 patients with metastatic adenocarcinoma of the prostate who were treated with exogenous testosterone, serious morbidity or mortality, seemingly due to the testosterone administration, occurred in eight cases (15%), and 87% experienced unfavorable subjective and/or objective responses. Moreover, in their review of the literature, they found reports on an additional 138 patients. They found that unfavorable subjective and/or objective responses occurred in 93% of patients.

Since testosterone is a cofactor for the development of prostate cancer, a principal concern with testosterone supplementation is that such therapy may have a permissive effect on occult prostate cancer in hypogonadal elderly men. Indeed, many older men have occult, microscopic foci of prostate cancer[56,57]. Morgentaler and associates[58] investigated the prevalence of occult prostate cancer in 77 men (mean age 58 years) with low serum total testosterone or free testosterone levels. Prostate cancer was identified in 14% (11/77) of the entire group and in ten men (29%) aged

60 years or older. The median age for men with cancer was 64 years. No significant differences were noted between the cancer and benign groups with regard to PSA level, PSA density, prostate volume, total testosterone level, or free testosterone level. In these men with low total or free testosterone levels, digital rectal examination and PSA levels were insensitive indicators of prostate cancer. The clinical importance of these occult foci of prostate cancer is unknown. Indeed, autopsy series have shown a substantial incidence of clinically occult prostatic adenocarcinoma, ranging in some series from 30 to 67% depending upon age[59–61]. Moreover, there is an apparent rarity of testosterone therapy unmasking clinically occult prostate cancer, with only a few single cases and/or small series of instances reported[62–67]. While it is possible that such cases are underreported, it may also be that occult foci of well-differentiated prostate adenocarcinoma have limited invasive potential, irrespective of testosterone supplementation. The impact of androgen supplementation on otherwise latent foci of prostate cancer is unknown, but the majority of investigators agree that prostate biopsies are not justified prior to initiation of testosterone therapy in view of the potential morbidity and in the face of the recommended diligent monitoring of patients during testosterone treatment.

Further evidence that the prostate cancer risks from use of androgen replacement therapy may not be as great as postulated comes from several sources. Using PSA as a marker for prostate cancer, all trials have shown no change or only a modest (within normal range) increase in PSA after testosterone administration[65–67]. Of particular note are the data from a retrospective analysis reported by Gerstenbluth and colleagues[65]. They assessed the findings of 54 testosterone-treated hypogonadal men with erectile dysfunction, with a mean age of 60.4 years (range 42.0–76.0) and a mean follow-up of 30.2 months (range 2.0–82.0) on testosterone therapy. Mean pretreatment PSA was 1.86 ng/ml (median 1.01 ng/ml, range 0.0–15.80), which increased to a mean PSA level of 2.82 ng/ml (median 1.56 ng/ml, range 0.0–32.36, $p < 0.01$) with testosterone treatment. Of the 54 men included in this study, six (11.1%) required prostate biopsy while on testosterone therapy because of a rise in serum PSA above 4.0 ng/ml. One patient (1.9%) was diagnosed with prostate cancer.

Collectively, evidence based either on the prevalence of simultaneous development of prostate cancer or rise of PSA does not support the view that short-term treatment of hypogonadal elderly men with androgens has a causal relationship with prostate cancer. Larger experience, however, is needed.

DISCUSSION AND RECOMMENDATIONS

Androgen supplementation studies have been, in most cases, of short duration and lacked a control cohort and have been insufficiently powerful to evaluate the effects of testosterone replacement therapy on prostate adverse event rates. Therefore, it is not possible to make definitive statements about the effects of testosterone therapy on the incidence of prostate cancer or symptomatic BPH in the absence of large, long-term, placebo-controlled studies. Determining the long-term safety of testosterone treatment will be a formidable challenge. To detect a 30% difference in prostate cancer incidence rates between placebo- and testosterone-treated groups, Bhasin and coworkers[68] estimated that 6000 patients would need to be randomized and followed for an average of 5 years.

Whether clinical symptoms of urinary obstruction worsen in older men receiving testosterone supplementation remains a subject of great interest. It is well established that hypogonadal men receiving adequate androgen therapy develop a prostate with a volume similar to what would be expected from their eugonadal counterparts[47,49,50,69]. Clinical trials of testosterone treatment in aging men showed no difference between controls and testosterone-treated men in requirement for invasive procedures for BPH; however, study population size was relatively small and treatment time relatively short. Moreover, evaluation of markers of BPH has shown no significant rise with testosterone treatment[70]. Other studies examining prostate size have found that prostate size increases with age regardless of the patient's testosterone treatment status[71].

Prostate cancer screening should be completed prior to instituting testosterone therapy, and should include an evaluation of risk factors for prostate cancer and determination of symptom scores using either the IPSS or the American

Urological Association questionnaire. Serum PSA and digital rectal examination should be performed prior to the initiation of and regularly throughout the course of androgen supplementation. Androgen administration is absolutely contraindicated in men suspected of having prostate or breast cancer. Another absolute contraindication to testosterone supplementation therapy is severe bladder outlet obstruction due to an enlarged clinically benign prostate. On the other hand, for men who have been clinically cured of localized, favorable pathology prostate cancer by radical prostatectomy, testosterone supplementation may be an acceptable therapeutic approach if they have clinical manifestations of hypogonadism supported by endocrine evaluation. Anecdotal reports and small series of such patients have provided very preliminary evidence that testosterone treatment can be safely administered to this group with careful monitoring and follow up[72].

It is important to consider that PSA levels in hypogonadal men may be lower than those of eugonadal men, and may indicate incorrectly the absence of prostate cancer[58]. Serum PSA levels may increase slightly after testosterone replacement therapy is initiated[44,47,70,73], but patients in whom the serum PSA level increases excessively should be evaluated for prostate cancer in the event that an occult prostate cancer existed at the start of treatment.

SUMMARY AND CONCLUSIONS

Androgens are undoubtedly involved in the growth of benign prostatic nodules, as a permissive factor in the etiology of prostate carcinoma, and in the enhancement of the growth of active prostate cancer. Their role in the initiation of either disease is unclear. While a definitive conclusion regarding the long-term safety of androgen supplementation in aging men is not possible, available data support the safety of such treatment in the short term. No evidence of increased risk for clinical prostate cancer or symptomatic BPH has been found in trials of androgen replacement therapy lasting up to 3 years. Caution is still advised in the interpretation of these findings, as the studies producing data involved relatively small numbers of participants. Until large, long-term, placebo-controlled studies have been conducted and analyzed, questions about the long-term safety of testosterone supplementation therapy in older men will remain.

ACKNOWLEDGEMENT

Support for writing this review was provided by Solvay Pharmaceuticals, Inc., Marietta, GA.

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