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INVITED REVIEW

Male Endocrinology

Androgens and prostate disease

Lori A Cooper¹, Stephanie T Page^{1,2}

A growing body of literature has established the anabolic benefits of testosterone (T) therapy in hypogonadal men. However, there remains a paucity of data regarding the risks of exogenous androgen use in older men and the potential for adverse effects on the prostate gland. Whether T therapy in older, hypogonadal men might worsen lower urinary tract symptoms or exacerbate, unmask, or even incite prostate cancer development has tempered enthusiasm for T therapy, while known prostatic disease has served as a relative contraindication to T therapy. Androgens are necessary for the development and maintenance of the prostate gland. However, epidemiologic studies do not consistently find a positive relationship between endogenous serum androgen concentrations and the risk of prostate disease. Recent data demonstrate that 5 α -reductase inhibitors decrease the risk of low-grade prostate cancer, suggesting that modifying androgen metabolism may have beneficial effects on prostate health, yet similar reductions in high-grade disease have not been observed, thereby questioning the true clinical benefits of these agents for chemoprevention. Knowing how to best investigate the relationship between androgens and the development of prostate disease given the lack of large, randomized trials is difficult. Accumulating data challenges the assumption that alterations in serum androgens have parallel effects within the prostate hormonal environment or change androgen-regulated processes within the gland. Long-term intervention studies are needed to truly ascertain the effects of androgen manipulation on prostate tissue and disease risk. However, available data do not support the notion that restoring serum androgens to normal physiologic ranges drives prostate disease.

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INTRODUCTION

In 1935, Adolf Butenandt and Leopold Ruzicka independently but simultaneously synthesized testosterone (T), leading to their joint award of the Nobel Prize in Chemistry in 1939 (although Butenandt was forced to decline the honor by the Nazi government). Since the availability of synthetic T in the 1940s, worldwide use has grown markedly.¹ Despite the fact that prescriptions for T continue to climb,² to date there have been no large, randomized-controlled trials to definitively assess the risks and benefits of exogenous androgens in older men. While androgens clearly have attractive anabolic effects, whether these provide true health benefits remains unclear. Moreover, there remain significant concerns regarding the safety of androgens for hormone-sensitive tissues, particularly the prostate gland. Here, we review our current knowledge regarding the relationship between endogenous and exogenous androgens and prostate disease.

Testosterone replacement and aging: benefits

T levels are highest in men during their twenties and steadily decline 1%–2% per year thereafter.³ While serum total T concentrations decrease with age, prospective longitudinal studies demonstrate that declines in free testosterone (fT), the active hormone, may be even greater, attributable to the effects of aging and health status.⁴ Whether or not this decline in T represents pathologic, late-onset hypogonadism or simply normal aging is controversial, and current clinical recommendations for both the diagnosis and treatment of androgen deficiency rely upon a combination of biochemical and clinical criteria.⁵

The differences in reported prevalence of late-onset hypogonadism vary in part due to assay variation and methods and are further complicated by the differences in cohorts and the definition used for diagnosis. Assay heterogeneity in the quantification of serum T concentrations makes absolute biochemical criteria unfeasible. Particularly at concentrations below the normal range for healthy young men, platform assays used by some commercial laboratories to measure total T concentrations are inaccurate and lack reproducibility.⁶ Currently, quantification of serum T concentrations by liquid chromatography-tandem mass spectrometry is optimal. The Centers for Disease Control has recently offered a program to certify laboratories for T quantification,⁷ an effort that should greatly improve assay quality for those laboratories that elect to participate. Using data from the European Male Ageing Study, Wu *et al.*,⁸ consider late-onset hypogonadism to be defined as a total T level <320 ng ml⁻¹ and free T level <64 pg ml⁻¹, in conjunction with at least three sexual symptoms. In this cohort, 2.1% of men from age 40 to 79 years fit this definition. In contrast, in the Massachusetts Male Aging Study, the prevalence of men age 30–79 having a total T level <300 ng ml⁻¹, fT <50 pg ml⁻¹, and symptoms consistent with androgen deficiency was 5.6%.⁹

The administration of T therapy to older, hypogonadal men to reach serum concentrations consistent with those of young, healthy men has been shown in randomized controlled trials to consistently offer several benefits. These include improvements in muscle mass and strength, favorable changes in body composition, and improvements

¹Departments of Medicine, Division of Endocrinology and Metabolism, University of Washington, Seattle; ²University of Washington and Harborview Medical Center, Seattle, Washington, USA.

Correspondence: Prof. ST Page (page@uw.edu)

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in libido and sexual health. Snyder *et al.*¹⁰ demonstrated in a group of hypogonadal men >65 years old that those randomized to a 6 mg per day T patch for 36 months had significant reductions in fat mass and increased lean muscle mass compared with placebo-treated men. Similarly, in a study of 70 men >65 years old with low T levels, Page *et al.*¹¹ randomized subjects to receive either T enanthate 200 mg IM every 2 weeks, T enanthate plus finasteride (F) [to block conversion of T to dihydrotestosterone (DHT)], or placebo for 36 months. Compared to baseline assessments, those in the T and T plus F groups had improvements in timed functional tests and handgrip strength. Similar to the study by Snyder, there were also significant decreases in fat mass and increases in lean body mass in both groups treated with T compared to those on placebo. Favorable effects of T and T + F were also seen on total cholesterol and low-density lipoprotein, and there were significant benefits of T on bone mineral density at both the spine and hip in these older, community dwelling men with low T.¹²

While Wu *et al.*⁸ found that sexual symptoms are the most sensitive indicator of hypogonadism in older men (European Male Ageing Study), the effects of T therapy on libido and sexual function, while generally positive, are somewhat mixed. Cumulatively, the data points to the greatest response in men with the lowest baseline T levels and does not show a consistent dose response. A meta-analysis of 656 subjects treated with T or placebo for a median study length of 3 months showed T moderately improved sexual desire and function in men with baseline T levels <12 nmol l⁻¹, but these benefits were not seen in eugonadal men.¹³ Gray *et al.*¹⁴ examined T dose-response relationships on sexual function in older, healthy men. A significant dose effect of T on libido was observed in men who were sexually active at the start of the study, as well as a dose effect on the frequency of morning erections, which differs from effects seen in younger, healthy men. The reasons for the age-related differences on sexual function in response to T are unknown.

Positive effects of T on mood,^{15,16} cognitive function,¹⁷ and quality of life (QoL) have been noted in some studies but are not consistently observed. Cross-sectional data, such as the Longitudinal Aging Study in Amsterdam, have reported that symptoms of depression are higher in men with low free T levels.¹⁵ Controlled intervention trials examining the impact of T therapy on depression and cognition^{18,19} have been small and to date insufficient to support the use of T in the treatment of cognitive and mood disorders, even in the men with low serum T.¹⁹ The effect of T therapy on QoL measures is also difficult to discern. In a recent placebo-controlled trial of T therapy in frail, elderly men with low or low-normal T levels, significant improvements in strength, body composition, physical function, and QoL were observed in those men receiving T therapy for 6 months compared to placebo.²⁰ However, when this same group was followed-up 6 months post T therapy, these effects were not maintained.²¹ Improvement in health-related QoL measures were also demonstrated in a larger, double-blinded, placebo-controlled trial of 362 men with low to low-normal T after 6 months of therapy.²²

Perhaps the most compelling rationale to advance our understanding of the risks and benefits of T therapy are recent observations linking low T levels with increased risk of all-cause mortality in older men. The Rancho Bernardo Study followed older, community dwelling men for a mean of 11.8 years and observed that low serum T (T <241 ng ml⁻¹) was associated with a 40% greater risk of death compared to men with higher T levels.²³ At least two other large, prospective studies have reported similar results,^{24,25} and the CHIANTI study found that low levels of anabolic hormones (T, insulin-like growth factor-1, dihydroepiandrosterone-sulfate (DHEA-S)) were associated with significantly higher 6-year mortality.²⁶ Although long-term

intervention data regarding T therapy and mortality are clearly lacking, in an observational cohort of over 1000 hypogonadal male veterans, Shores *et al.*²⁷ observed that those men with low serum T who received T replacement had significantly decreased mortality compared with those men who had not received T, even after adjusting for multiple co-morbidities including age, diabetes, body mass index, and coronary artery disease. Together, these observational studies suggest that low T levels may predispose men to early mortality and support the possibility that T replacement may be beneficial in selected patients.

In summary, both cross-sectional and intervention data suggest that T therapy in older men with low serum T has beneficial effects on body composition, strength, bone mineral density, and libido. However, evidence that T therapy reduces morbidity and mortality lacking. Ultimately the benefits of T therapy need to be considered against potential risks of therapy. But what are those risks? Similar to the issue of beneficial effects, evaluation of the risks of T therapy has focused on signs and symptoms rather than on disease endpoints. T therapy increases hemoglobin and hematocrit²⁸ (although this can be a benefit in some cases) and may worsen obstructive sleep apnea.²⁹ The greatest concerns regarding T therapy and disease are the potential to increase cardiovascular disease risk and prostate cancer incidence. Exogenous T can mildly reduce total and high-density lipoprotein cholesterol concentration,²⁸ changes that might have negative effects on cardiovascular disease risk, and a recent small intervention study in frail older men suggested that the cardiovascular event rate might be increased by T therapy in select groups of men.³⁰ In contrast, no controlled intervention studies to date have reported an increased risk of prostate cancer or prostate disease in men receiving T therapy compared with control subjects. But due to issues of study power and duration, the relationship between T therapy and prostate disease risk is a fundamental and unanswered question in the field. No studies to date have been powered to discern the risk, if any, of T therapy and prostate disease; moreover, no such trials are currently underway. Thus, data regarding T therapy and prostate disease risk are at least a decade away. In the interim, however, prescriptions for T have steadily risen. A recent examination of prescribing habits in the United Kingdom showed the number of prescriptions for T has increased 90% from 2001 to 2010.³¹

Since appropriate evidence from randomized-controlled trials is lacking, what is the best evidence available regarding T therapy and prostate disease? Conventional teaching has been that pre-existing benign prostatic hypertrophy (BPH) and prostate cancer may be aggravated by T therapy, given that androgen diminution and withdrawal are the mainstays of therapy for these diseases. However, the applicability of these observations, accrued in the setting of disease, to the physiology of the healthy prostate is unclear. Here, we will review both observational data as well as clinical intervention trials involving T therapy and prostate responses. In addition, we will discuss recent data involving the intraprostatic response to systemic androgen manipulation. Further investigation into the hormonal and cellular pathways regulating prostate disease processes is crucial to our understanding of the relationship between T therapy and prostate disease.

Androgen deprivation and prostate cancer

Androgens are an absolute requirement for the development and maintenance of male reproductive tissues including the prostate. The prostate fails to develop in men with mutations in the androgen receptor (AR) or the enzyme 5 α -reductase type 2 (5 α R2), which is highly expressed in the prostate and converts T to the more potent androgen, DHT.³² BPH results predominantly from expansion of the

prostate stroma, under the influence of DHT.^{33,34} Prostate cancer, on the contrary, is a disease of the prostate epithelium, although stromal factors appear to play a role in neoplastic transformation.³⁵

In 1941, Huggins and Hodges³⁶ demonstrated the sensitivity of prostate carcinoma to androgens ultimately garnering the Nobel Prize in 1966 for their work. Their seminal paper, and hundreds of studies that have followed, demonstrate that androgen withdrawal results in initial regression of essentially all prostate cancers, albeit for a finite period of time, with the ultimate development of castration-resistant disease. Thus, androgen deprivation therapy, via either orchidectomy or, much more commonly, use of a gonadotropin releasing hormone (GnRH) agonist to suppress production of luteinizing hormone has become the cornerstone of therapy in the treatment of metastatic prostate cancer. Newer agents, such as abiraterone, which block androgen synthetic pathways, have added clinical benefit in disseminated disease, demonstrating that even in “castration-resistant disease” androgens may still be supporting prostate cancer growth.³⁷ These data support the notion that prostate cancer, in most cases, is a hormone sensitive disease.

While there is clear evidence that prostate cancers can respond to androgen withdrawal, Huggins and Hodges' conclusions regarding the sensitivity of prostate cancer to exogenous T are more difficult to interpret and have been the subject of recent scrutiny and debate.³⁸ Indeed, the extrapolation of their findings in individuals with metastatic prostate carcinoma to the natural history of low-grade prostate carcinomas, as well as healthy prostate tissue, likely oversimplifies the complexity of normal prostate physiology. Similarly, in 1981, a retrospective analysis helped to potentiate the notion that exogenous T might accelerate prostate cancer. Fowler and Whitmore⁴⁰ reported a series of 52 men with metastatic prostate cancer who had received exogenous T, 45 of whom had reported unfavorable effects (subjective symptoms or objective progression of disease), most of which reversed again following cessation of T administration. All but four of these men had undergone prior androgen deprivation either by castration or estrogen administration. Interestingly, only one of the four men who did not undergo prior castration had an early, unfavorable response, and the remaining three continued to receive T. In this retrospective series, it was concluded that T administration resulted in rapid disease progression due to the inherent androgen responsiveness of prostate cancer, although this effect was less clear in men with normal pre-treatment androgen production.⁴¹

The concept that exogenous T “feeds the fire” of prostate cancer has been challenged by subsequent retrospective analyses. Morgentaler *et al.*³⁹ reported a higher than expected prevalence of occult prostate cancer in a retrospective series of 77 men with low serum T concentrations, normal prostate-specific antigen (PSA), and normal digital rectal exams. This report was followed with additional retrospective analyses of men with prostatic intraepithelial neoplasia treated with T therapy for 1 year and having no greater increase in PSA or significantly increased risk of cancer than men without prostatic intraepithelial neoplasia,⁴² and a recent case series suggesting the safe treatment of men with a history of prostate cancer with T therapy.⁴³ Others have also reported retrospective series of men safely treated with T therapy, following treatment for prostate cancer,^{44–46} suggesting that while exogenous T may raise serum PSA concentrations, in appropriately selected subjects, T therapy may not increase the risk of clinically significant disease recurrence.

While such retrospective reports are provocative, none of these analyses directly address the impact of T therapy on healthy prostate tissue and on long-term prostate disease risk. The response of prostate

cancer to androgen deprivation therapy is unequivocal, but whether the converse is true, that exogenous T accelerates prostate cancer risk, disease, or recurrence has been called into question. Without appropriately designed and powered intervention studies, the true risk of T therapy on prostate disease is unknown. However, an understanding of the relationships between endogenous androgens and prostate cancer risk, as well as the prostate response to changes in the serum hormonal milieu, may inform current clinical practice and the design of future trials.

Epidemiology linking endogenous androgens and prostate disease

If increases in exogenous androgens increase prostate disease risk, one would expect that higher endogenous androgen concentrations would be positively associated with prostate cancer risk. Most studies to date have failed to find a strong relationship between serum T levels and prostate cancer. However, such longitudinal studies are complicated by many uncontrolled variables including the length of follow-up, sample acquisition (single versus repeat samples, fasting, time of day, etc.), sample storage, assay characteristics, and disease reporting during follow-up. The Baltimore Longitudinal Study on Aging⁴⁷ has the longest such follow-up and includes serial androgen measures performed over a period spanning nearly 40 years. In this cohort, Parsons *et al.* found that higher calculated fT levels were positively associated with prostate cancer risk (relative risk 2.59), while hypogonadal men had 49% lower risk of prostate cancer compared to age-matched, eugonadal men. Further analysis of men in the Baltimore Longitudinal Study on Aging⁴⁸ examined the relationship between serum T concentrations and high-risk prostate cancer, defined as death from prostate cancer, a PSA level ≥ 20 ng ml⁻¹, or a Gleason score ≥ 8 . The incidence of high-risk prostate cancer among men >65 years was significantly increased for those in the highest tertile of fT concentration (hazard ratio 2.07), although this was not true for men <65 years. Adding to the concern that higher endogenous androgen levels contribute to prostate disease, the Rancho Bernardo Study⁴⁹ found a positive relationship between baseline serum DHT levels and the development of BPH over 8 years of follow-up. Of note, however, is that in a subsequent analysis, among the 158 surviving participants without prostate cancer in this cohort the relationship with serum DHT did not persist, and in fact an inverse relationship was noted at 20 years between the development of lower urinary tract symptoms and serum bioavailable T.⁵⁰

In contrast to the aforementioned publications, a number of studies have failed to find a positive association between endogenous serum androgen concentrations and the development of prostate disease.^{51,52} In an effort to resolve these conflicting epidemiologic studies and increase the power of the analyses, the Endogenous Sex Hormones and Prostate Cancer Collaborative Group pooled data from 18 prospective studies of 3886 men with incident prostate cancer and 6438 control men.⁵³ In this collaborative analysis, serum concentrations of T, free T, DHT, DHEA-S, androstenedione, androstanediol glucuronide, estradiol, and calculated free estradiol, whether high or low, were not found to be associated with the risk of prostate cancer. While this analysis has some limitations, the pooled data clearly refute the notion that endogenous serum androgens are a strong, modifiable driver of prostate cancer development.⁵⁴

Although serum androgen concentrations are not clearly linked to the development of prostate disease, what about the concentration of androgens within the gland itself? Recent data from large, randomized-controlled trials^{55,56} have demonstrated that interference with the intraprostatic hormonal environment may reduce the incidence of some prostate cancers. Before abandoning a

hormone-driven hypothesis regarding androgens and prostate disease altogether, it is important to consider the impact that androgens, and the manipulation of androgen metabolism, have on prostate growth and the intraprostatic hormone environment.

Intervention trials of testosterone replacement and effects on prostate volume and prostate-specific antigen

Small trials of androgen replacement in T deficient men have been reassuring regarding prostate health. While underpowered to look at hard clinical endpoints, numerous trials of T therapy have included clinical surrogates of prostate effects including prostate volume, PSA, and lower urinary tract symptoms and obstruction. Correction of biochemical hypogonadism can be associated with mild increases in prostate volume and PSA. Behre *et al.*⁵⁷ compared prostate volume, serum PSA, and uroflow parameters in three groups of age-matched men with either newly diagnosed hypogonadism (never been on T therapy), hypogonadal men with at least 6 months of T therapy, or healthy, eugonadal men. Untreated hypogonadal men had significantly lower prostate volumes and PSA in comparison to hypogonadal men on T therapy and eugonadal, age-matched controls. However, there were no significant differences in prostate volume, PSA, or uroflow parameters between hypogonadal men on T therapy and healthy controls. Further, studies⁵⁸ looking at the effects of T therapy on PSA also demonstrated only minor elevations in PSA in hypogonadal men treated with T over a period of 30 months, and these changes were manifested largely within the first 6 months of therapy. Consistent with these results, Bhasin *et al.*⁵⁹ showed that in 60 older men treated with a GnRH agonist to suppress endogenous T and then given back T in dosages ranging from 25 to 600 mg weekly for 20 weeks, there was a dose-dependent correlation with T and free fat mass and muscle strength, but not with PSA. Together these studies support the concept that correction of hypogonadism to eugonadal levels has mild prostate effects, but that these effects are not cumulative over time or with dose, but rather result in a new equilibrium akin to that of eugonadal, age-matched men.

An initial meta-analysis of randomized, controlled trials of androgen replacement in older hypogonadal men found no overall increase in the incidence of prostate cancer, symptoms associated with BPH, clinically significant PSA increases, PSA levels prompting biopsy, or prostate biopsies performed in the combined treatment group compared to placebo.⁶⁰ More recently, Fernandez-Balsells *et al.*²⁸ looked in further detail at compiled data from 51 studies of T therapy ranging from 3 months to 3 years in duration. While significant effects of T were seen on hematocrit and high-density lipoprotein cholesterol, there were no significant increases in prostate-related adverse events in those on treatment versus controls (including PSA, need for prostate biopsy, incidence of prostate cancer, or changes in lower urinary tract symptoms). While the quality of evidence included in the meta-analysis was influenced by the short duration of exposure in the studies included, it nevertheless is reassuring that no large effect on prostate health has been overlooked in the trials of T therapy conducted to date.

Although limited intervention trials have not demonstrated an increase in prostate-related adverse events in men receiving testosterone replacement therapy, determining how to best monitor men for prostate health while on T-therapy is difficult, and current guidelines are not evidence-based. Unfortunately, simply following a PSA in men at baseline and following initiation of T therapy is not sufficient, as PSA is an androgen-responsive gene likely to modestly increase when serum T levels rise, potentially leading to unnecessary prostate biopsies. Moreover, the routine use of PSA to screen for prostate cancer is no longer recommended,⁶¹ since large trials have failed to

show a mortality benefit in low-risk individuals.^{62,63} We believe these new recommendations should influence clinical decisions regarding obtaining a baseline PSA in many men being considered for T therapy. In an effort to minimize the potential for invasive testing and the overdiagnosis of prostate cancer in men on T therapy, the Endocrine Society, in their 2010 guidelines, recommend following the PSA in those individuals >40 years of age who have a baseline PSA value, and using a rise in >1.4 ng ml⁻¹ per year as a trigger for more invasive testing, noting that the average increase in PSA for men on T therapy is approximately 0.5 ng ml⁻¹.⁵ Given the recent shift away from PSA screening in most men, and the lack of data linking T therapy and prostate cancer, we suggest that in men with a known, organic cause of primary or secondary hypogonadism (i.e., genetic abnormality, pituitary surgery or defect, drug effect such as long-term opiates, etc.), who receive T therapy targeted to the normal range for healthy men, consensus guidelines for use of PSA screening be followed. For these men, a baseline PSA should only be obtained after a full discussion with the patient regarding the pros and cons of PSA screening and not be offered to men <55 years of age. In men with risk factors for prostate cancer, those treated for late-onset hypogonadism, and all men initiating T therapy ages >55 and <70 years of age we follow the Endocrine Society guidelines as outlined above, obtaining a baseline PSA and then monitor PSA after 4–6 months and then annually thereafter, and recommend a prostate biopsy if we observe a PSA increase of >1.4 ng ml⁻¹ per year. The critical issue in all cases is having an informed and documented communication process surrounding the pros and cons of PSA screening to ensure that each individual realizes the risk of biopsies, overdiagnosis, and the lack of clarity regarding the relationship between T therapy and prostate cancer risk. Hopefully, with the results of the ongoing large, randomized trial of T therapy in older men⁶⁴ becoming available over the next few years, the approach to monitoring prostate health on T therapy can be further refined.

The limited data available regarding the effects of supraphysiologic dosing of androgens on prostate health also do not point toward a significant role for circulating androgens in promoting prostate hyperplasia or cancer. Young men who chronically abused anabolic steroids for athletic purposes had similar prostate volumes and PSA levels compared to age-matched controls.⁶⁵ Similarly, healthy young men who are acutely administered intramuscular T at doses as high as 500 mg weekly (fivefold the physiologic replacement dose) for 15 weeks did not have significant changes in PSA or prostate volume.⁶⁶ In two dose-response studies of T administration after GnRH agonist treatment, no dose-related increases in PSA or prostate volume were reported over 16–20 weeks of treatment. Furthermore, in both of these studies PSA levels were reduced when T was decreased below baseline but did not increase with increases in T above baseline.^{59,67,68} In summary, in studies of high-dose T supplementation, prostate-related measures do not appear to be dose sensitive to serum T concentrations above approximately 300 ng ml⁻¹, the lower limit of the normal range for healthy young men.

What about giving androgens to men with known prostate enlargement? Arguably, this might be a strategy for unveiling prostate effects in a more androgen-sensitive population. Men with symptomatic BPH and LUTS have generally been excluded from studies of T therapy with concern for symptom exacerbation and even urinary retention due to further androgen-induced increases in prostate volume. Several recent studies have suggested that this is not a clinically significant concern. We recently assessed the effect of T therapy in older men with symptomatic BPH who had enlarged prostates (>30 cc by magnetic

resonance imaging) and hypogonadism. Subjects were randomized to receive T therapy in combination with placebo or the 5 α R inhibitor dutasteride (to inhibit the conversion of T to DHT) for 6 months. Despite correction of biochemical hypogonadism, neither group experienced an increase in prostate volume nor International Prostate Symptom Scores with treatment (the latter of which actually improved slightly in both groups), and there were no prostate-related adverse events. Moreover, the groups receiving T in combination with dutasteride had a significant decrease in both PSA and prostate volume compared to baseline.⁶⁹ Overall, these data suggest that the effect of normalization of serum T levels in older, hypogonadal men on prostate volume is probably clinically safe, even in the setting of pre-existing prostate enlargement, and support the hypothesis that the relationship between serum T concentrations and prostate growth is likely non-linear.

5 α R inhibitors and prostate disease

Due to the high levels of expression of 5 α R, the androgen environment within the prostate is unique. Three isoforms of 5 α R have been described.⁷⁰⁻⁷² The prostate expresses high levels of the type 2 5 α R and is thus capable of *in situ* conversion of T to DHT. This conversion results in intraprostatic DHT concentrations that are ~ 10-fold higher than T and 100-fold greater than serum DHT.³³ Conversely, in serum T concentrations are 10-fold greater than DHT concentrations. Thus, in the healthy human prostate, a gradient of both DHT and T is maintained relative to serum. Since DHT binds with higher affinity to the AR, the high levels of DHT relative to T in the prostate might be considered an amplification of androgen signaling within the tissue compared to serum. Thus, inhibition of 5 α R more profoundly affects the prostate as compared to other androgen-sensitive tissues that rely on T for androgen signaling. Currently, two 5 α R inhibitors are available for clinical use. Finasteride, which is specific for the type 2 isoform of 5 α R, and dutasteride, which inhibits both type 1 and type 2 isoforms. Treatment with a 5 α R inhibitor results in very little increase in serum T levels, while serum DHT levels are reduced by 70% (finasteride) to 95% (dutasteride).^{73,74} Large, randomized, controlled trials have demonstrated that both F and dutasteride produce significant prostate shrinkage and lower serum PSA when taken by men with BPH.⁷⁵⁻⁷⁹

Recent placebo-controlled trials with 5 α R inhibitors have found that long-term treatment with 5 α R inhibitors in older men can reduce the incidence of some prostate cancers. The Prostate Cancer Prevention Trial (PCPT) demonstrated that administration of F to older men results in a 25% reduction in the incidence of prostate cancer compared to placebo.⁸⁰ Similar risk reduction in prostate cancer incidence was reported for dutasteride in the Reduction by Dutasteride of Prostate Cancer trial.⁵⁵ In the PCPT, the overall reduction in prostate cancer incidence resulted from a reduction in the incidence of low-grade disease, while higher-grade prostate cancers were paradoxically increased in the treatment group. *Post hoc* analyses of these specimens has suggested that this increase in high-grade disease may have been the result of ascertainment bias due in part to decreased prostate volume,^{80,81} but it is conceivable that low androgen levels within the gland resulted in a de-differentiation of pre-malignant lesions.^{82,83} In Reduction by Dutasteride of Prostate Cancer, 6729 men age 50-75 years old with PSA levels 2.5-10.0 ng ml⁻¹ and negative prostate biopsies 6 months prior to enrollment were randomized to receive either placebo or dutasteride over a 4-year period with prostate biopsies performed at 2 and 4 years. Over the 4-year period of time, dutasteride provided a relative risk reduction of 22.8% over placebo, similar to that reported for the PCPT. However, like the PCPT, there was a higher risk of high-grade disease in those men treated with a 5 α R inhibitor in years 3 and 4

despite clear reductions in risk of low-grade disease with treatment.⁸⁴ Together, these large trials support the concept that reductions in androgens may prevent some prostate cancers in older men. The mechanism through which this might occur has not been determined but theoretically could result from the impact of reduced intraprostatic DHT concentrations on prostate epithelial cell apoptosis.^{85,86}

One possible strategy for specifically reducing the prostate effects of T therapy while retaining the anabolic effects of T in other tissues has been to combine T with a 5 α R. Based upon data from PCPT and Reduction by Dutasteride of Prostate Cancer, it is possible that such a strategy might provide some chemopreventative effects as well. Tenover and his colleagues demonstrated this to be an effective strategy for T therapy using prostate volume and PSA as markers of prostate of response. They demonstrated a neutralizing effect on prostate growth when T was combined with F over a 3 year period, despite maintaining favorable effects of T replacement on bone,¹² body composition, and strength.¹¹ Bhasin *et al.*⁸⁷ recently expanded on these findings, demonstrating that the addition of dutasteride to T did not impact the dose-response-related anabolic endpoints associated with T administration.

In summary, 5 α R inhibitors significantly decrease prostate size, PSA, and the incidence of low-grade prostate cancer in older men. Small studies conducted during the development of 5 α R inhibitors demonstrated that these agents potentially alter the intraprostatic androgen environment. In men with BPH, administration of a 5 α R inhibitor markedly reduces intraprostatic concentrations of DHT, similar to the effects of these agents on serum concentrations of DHT. However, in contrast to the marginal effects observed on serum T levels, inhibition of 5 α R results in a marked, compensatory increase in intraprostatic T concentrations.⁸⁸⁻⁹¹ These alterations in intraprostatic androgens are presumed to be the mechanism, whereby 5 α R inhibitors exert their clinical benefits. It is of interest, therefore, to examine the effects of androgen manipulation in other clinical settings on the intraprostatic hormonal milieu, in order to further our understanding of both prostate physiology and perhaps aid in the prediction of the effects these interventions may have on disease.

Intraprostatic androgens

The question of whether alterations in serum androgens are mimicked within the intraprostatic hormonal milieu may be relevant when considering the risks and benefits of T therapy in older men. Recent data suggest that while large decreases in serum androgens, such as in the setting of medical castration, also lower intraprostatic androgens, the degree of change in each compartment may not be equivalent.⁹²⁻⁹⁴ Moreover, two recent studies examining the effects of exogenous androgens on intraprostatic hormone levels have failed to show parallel increases in serum and prostate androgen concentrations.^{95,96}

Provocative studies demonstrating high concentrations of intraprostatic androgens in castration-resistant, metastatic prostate cancers despite longstanding castration^{93,94} have complimented the growing body of literature examining the impact of 5 α R inhibitors on intraprostatic androgen concentrations. In both cases, manipulation of serum androgens was not mirrored within the prostate. In an observational study, Mohler *et al.*⁹³ found high levels of T within these prostate tumors, equivalent to levels in non-neoplastic prostate tissue, despite serum T levels in the castrate range, suggesting the possibility of intratumoral androgen synthesis. Intraprostatic androgen synthesis has been postulated by others and a number of groups have demonstrated the expression of androgen-synthetic enzymes within the prostate.⁹⁷⁻⁹⁹ In the healthy prostate, treatment for 1 month with

a potent GnRH antagonist⁹² decreased serum T levels by 94% and decreased intraprostatic androgen concentrations, but only by 70%–80% compared to controls. Androgen-regulated gene expression, PSA, and AR expression were also maintained compared to controls. Thus, while medical castration profoundly affects serum androgen levels, there is a relative preservation of androgen concentration and action within the prostate gland.

Accumulating data suggest that changes in the intraprostatic hormonal milieu resulting from androgen supplementation may not be dose-dependent. Studies in rodents suggest that supraphysiologic levels of circulating T and DHT in intact rats do not result in prostate growth.^{100,101} In an elegant study by Wright *et al.*¹⁰² castrated rats were implanted with increasing doses of T or DHT pellets for 7 days. Despite a nearly 100-fold increase in serum T or DHT concentrations at the maximum dose, intraprostatic DHT increased only 10-fold and intraprostatic T was no different compared to placebo-treated castrate rats. Of note, when the 5 α R inhibitor F was included with T treatment, intraprostatic DHT levels remained near those of placebo-treated, castrate controls even at the highest dose of T administered. Moreover, measures of prostate androgen response (prostate weight, duct mass, and deoxyribonucleic acid content) were twofold to threefold more responsive to intraprostatic DHT compared to T, demonstrating the greater potency of DHT within prostate tissue. The authors concluded that there was a threshold of intraprostatic T and DHT required to initiate prostate regrowth in their model. In addition, they postulated that the inclusion of a 5 α R inhibitor to T treatment increased the serum T level at which these intraprostatic androgen thresholds were reached by 10–15-fold by blocking not only conversion of T to DHT, but also by inhibiting androgen accumulation within the prostate at low serum T concentrations.¹⁰² The mechanism by which this accumulation occurs was not elucidated.

In humans, two recent studies have evaluated the effect of exogenous androgens on intraprostatic androgen concentrations. Marks *et al.*⁹⁵ studied 40 elderly men with low serum T who received either placebo or low-dose T replacement for 6 months. Prostate core biopsies were obtained at baseline and following treatment. T replacement raised serum T levels by 2–2.5-fold while keeping them well within the normal range for healthy young men, but did not raise intraprostatic T or DHT compared to baseline and to the placebo group. Likewise, markers of androgen action, including prostate epithelial cell gene expression and proliferation, were no different between groups or compared to baseline. Only serum PSA, but not prostate volume, increased from baseline in the T-treated group, while the percentage of atrophic glands tended to decrease with T treatment. While this important trial was reassuring regarding the impact of androgen replacement on the prostate, it was somewhat limited in terms of both the small number of subjects and the modest level of T exposure in the treatment group. A second study looked at the shorter-term effects of exogenous DHT on intraprostatic hormone levels in healthy men.⁹⁶ Consistent with results from Marks *et al.*⁹⁵ significant increases in serum DHT concentrations, more than seven fold normal serum concentrations, had no impact on intraprostatic DHT and T levels, and no significant effects on PSA and prostate volume. Together, these studies have led to the proposal that the prostate may harbor a “buffering” system which allows for maintenance of intraprostatic androgen levels despite fluctuations in serum levels, at least within the normal range of serum T concentrations. Both of these studies are consistent with the concept that intraprostatic androgens are not concomitantly increased when serum androgen levels are raised.

Morgentaler and Traish¹⁰³ have recently proposed a model to explain these and other observations wherein the prostate appears to

be sensitive to low, but not high levels of circulating androgens. The “saturation model” proposes that the prostate is sensitive to very low concentrations of circulating androgens, but that once maximal AR binding is achieved, which occurs at relatively low concentrations of circulating T, further increases in serum T have little impact. This model is consistent with studies in rodents.^{100–102} It can also explain the ability of low levels of intraprostatic androgens to maintain prostate gland size and PSA.¹⁰⁴ It is also consistent with observations by Fowler and Whitmore,⁴⁰ wherein men with metastatic prostate cancer given T who had been previously treated with castration had worsening of disease, whereas those without prior castration did not. The saturation model, however, does not explain why such saturation responses are not observed in other tissues such as muscle and bone, which have more linear dose-responses to escalating doses of exogenous T. Further studies are needed to substantiate the saturation model before it is used as the basis for therapeutic decision making.

CONCLUSION

Male hypogonadism has been associated with many comorbidities, and T therapy can offer several benefits including improvements in strength, bone mass, and some aspects of sexual function. While new evidence links low T levels and mortality, there is persistent concern that T therapy will stimulate the development of prostate carcinomas. The real risk of prostate disease posed by the administration of T therapy is unknown. Additionally, more studies are needed to determine the differences in serum and intraprostatic androgens and what effects long-term manipulation of the intraprostatic hormonal environment may cause. Despite the elegant explanation offered by the saturation model, its relevance to both normal and neoplastic prostate physiology is unproven at this time.

Currently, a large, multicenter trial looking at 800 hypogonadal men on T therapy (The T Trial in Older Men)⁶⁴ is underway to assess the benefits of T therapy in older men, yet it is not powered to assess risk. There is little data to support the withholding of T therapy on the basis of concern for precipitating prostate cancer. Both intervention data and physiology studies point to minimal effects on the prostate gland when serum T levels are increased to the mid-normal range with T therapy. However, given the paucity of hard data, current clinical guidelines are appropriately conservative⁵ in implementing its use only in those without a personal history of prostate cancer. Thus, an individualized care plan to assess the possible risks and benefits of T therapy for each patient is critical to optimizing the use of androgens in male health.

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COMPETING INTERESTS

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