Review Article

Testosterone replacement and prostate cancer

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ABSTRACT

This article is intended as a review of the available clinical data outlining the risks and benefits of testosterone (androgen) replacement therapy, specifically addressing the issue of the relationship between exogenous androgen administration and prostate cancer risk. There is controversy over whether androgen replacement is a risk factor for incident prostate cancer. Our review of current clinical information revealed that to date, no study or review has definitively shown that androgen replacement therapy is an independent risk factor for development of prostate cancer. Androgen administration seems to be beneficial in decreasing fatal cardiovascular events, body fat mass, and insulin resistance. Overall, the current clinical data seems to suggest that androgen replacement is an appropriate therapeutic option for men with symptomatic hypogonadism provided that patients continue to receive regular prostate screenings.

Key words: Androgen replacement, hypogonadism, prostate

INTRODUCTION

Hypogonadism is defined as a low serum testosterone level and consists of a number of clinical symptoms such as depression, lack of libido, and decreased bone mineral density. Hypogonadism can adversely impact a number of different organ systems and may cause a decrease in the quality of life for affected individuals.[1,2] It is estimated that only 5% of the 2-4 million affected men in the United States receive therapy.[2] This condition is often referred to as andropause when it occurs in an older male. In men with hypogonadism, returning serum testosterone to normal levels with testosterone replacement therapy can produce improvements in cognition, mood, sense of wellbeing, energy level, sexual function, bone mineral density, erythropoiesis, and muscle strength. Taken together, these benefits resulted in a marked increase in the popularity of testosterone replacement in the United States. The sale of prescription testosterone products has increased nearly 500% from 1993 levels of sales. However, many urologists are reticent to prescribe testosterone replacement in men who have had definitive therapy for prostate cancer or in men who are at high risk for new prostate cancer. This hesitation is due to the previously demonstrated benefits of testosterone deprivation in prostate cancer. This article is intended as a review of relevant clinical information regarding the impact of testosterone on the prostate, the relationship between serum testosterone and prostate cancer, and the benefits of testosterone replacement for men with symptomatic hypogonadism.

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RELATIONSHIP OF TESTOSTERONE AND PROSTATE CANCER

Huggins and Hodges demonstrated in 1941 that reducing testosterone levels by castration caused regression of metastatic prostate cancer and that administering testosterone promoted the growth of prostate cancers.[3] To this day, however, there is no conclusive evidence of a clear-cut correlation between high serum testosterone levels and prostate cancer risk.

Since prostate cancer is known to be androgen-dependent, there is concern that small, previously undetected tumors may progress to overt disease in the presence of exogenous testosterone or even under the influence of high levels of endogenous testosterone. The question of whether testosterone stimulates the development of prostate cancer remains controversial.

A number of studies[4-6] have been conducted to examine this controversy, but these studies have failed to demonstrate an association between prostate cancer and high serum testosterone levels. The Endogenous Hormones and Prostate Cancer Collaborative Group[7] published an analysis of 18 prospective studies on serum androgen levels and prostate cancer risk in 2008. The study included 3866 men with incident prostate cancer along with 6438 controls, representing over 95% of all published data worldwide. The study's main finding indicated that there was no association between prostate cancer and pre-diagnostic serum levels of free testosterone, total testosterone, dihydrotestosterone (DHT), androstenedione, DHEA-S, Adiol-G, free estradiol, or total estradiol. In fact, older men with the highest risk of prostate cancer have the lowest serum testosterone levels.

TESTOSTERONE LEVELS AND PROSTATE CANCER AGRESSIVENESS

Some prior studies have raised concerns that prostate cancer risk may be increased in men with low levels of testosterone. In hypogonadal men with PSA less than 4.0 ng/ml, prostate biopsy revealed cancer in 15%, with double the risk of cancer in men with greater reductions in testosterone as compared to men with more mild reductions. Men with low testosterone levels have also been shown to have worse prognoses in prostate cancer with higher-grade cancers and higher stage at presentation.[8,9] One possible explanation is that low levels of testosterone do not activate the androgen response elements in the PSA promoter. Men with low testosterone levels would then have a greater latency period before diagnosis because their PSA would rise more slowly.

Based on surgical samples, the preoperatives serum testosterone levels correlated with tumor stage in men who underwent radical prostatectomy. This suggests that lower concentrations of testosterone are associated with a higher probability of finding advanced-stage cancer. [10] In fact, 75% of men with testosterone levels at or below 2.5 ng/ml had either advanced disease locally or distant metastatic prostate cancer. A low testosterone value (below 2.5 ng/ml) was an independent predictor of advanced disease.

In the Prostate Cancer Prevention Trial (PCPT),[11] finasteride reduced prostate cancer risk by 25%. This finding supports the role of DHT in the development of prostate cancer. The associated increase in detection of high-grade cancer suggested the possibility that DHT-lowering agents had a lesser effect on reducing high-grade prostate cancer. However, additional analyses suggested that the higher risk of high-grade prostate cancer in patients taking finasteride might have been due to increased sensitivity of prostate biopsy in those patients.[12] The fact that PSA production is androgen-dependent further confounds the already controversial role of low testosterone and prostate cancer detection. PSA levels without concurrent testing of serum testosterone levels may limit the utility of the PSA test in diagnosing some prostate cancers.

THE EFFECT OF TESTOSTERONE REPLACEMENT THERAPY ON PSA

Several studies have been conducted to analyze the impact of testosterone replacement on PSA. Except for a rise in PSA shortly after initiating testosterone therapy, there is no increased risk of developing prostate cancer while on testosterone replacement therapy.[13,14] In a retrospective study reported by Gerstenbluth *et al.*,[15] 54 hypogonadal men with erectile dysfunction received intramuscular testosterone (mean age 60.4 years and mean follow-up 30 months). Testosterone levels in these patients rose from a pretreatment mean of 1.89 ng/ml to a mean of 9.74 ng/ml in the upper range of normal physiologic values. The PSA values rose from a pretreatment mean of 1.86 ng/ml to 2.82 ng/ml while on testosterone therapy. Of the 54 patients, one was diagnosed with prostate cancer. The authors concluded that testosterone therapy is associated with a slight increase in PSA, but is not associated with any short-term increases in prostate cancer risk in hypogonadal men with erectile dysfunction. Since PSA production is androgen-dependent, the exogenous androgen provided during testosterone replacement therapy may actually increase the likelihood of diagnosing prostate cancers that were being masked my low PSA production in men with testosterone deficiencies. McLaren *et al.*,[16] conducted a retrospective study of 85 patients who received testosterone replacement for symptomatic androgen deficiency. They reported little change in PSA levels in patients receiving testosterone for over two years despite increases in average levels of both free and total testosterone.

Currently available data suggests that even hypogonadal men without prostate cancer will exhibit detectable (albeit small) increases in PSA during testosterone therapy. Patients with large PSA changes should be evaluated for the development of prostate cancer. Current practice guidelines suggest that hypogonadal patients with normal PSA levels should have their PSA rechecked at three months, one year, and every 6 to 12 months thereafter while on testosterone replacement.[2,17] If the PSA is less than 4.0 ng/ml but rises by 1.5 ng/ml or more in a year, or 0.75 ng/ml per year over two years, further evaluation for prostate cancer including biopsy should be discussed. The role of PSA velocity as an indication for prostate biopsy is still controversial. Data from the Prostate Cancer Prevention Trial[11] indicated an increased sensitivity when PSA velocity was used as an indication for biopsy. However, using a PSA velocity as an indication reduces sensitivity and increases the number of unnecessary biopsies.[18,19] Finally, biopsies should be offered to any patient with a PSA level above 4.0 ng/ml.[20]

PROSTATE CANCER IN MEN RECEIVING EXOGENOUS TESTOSTERONE

To date no study or review has documented any direct evidence that testosterone therapy increases incident prostate cancer risk. However, it is still difficult to argue that androgen replacement is safe since no long-term studies have been completed in large populations receiving exogenous androgens over many years. The question of whether androgen replacement increases prostate cancer incidence in an aging population has yet to be answered. The Institute of Medicine, recognizing the need for additional clinical trials to clarify the risks and benefits of testosterone replacement therapy (TRT), formed a committee to evaluate the present status of TRT in 2003.[21] This was the most recent statement on the issue of TRT from the Institute of Medicine.

Even studies of TRT in men with high risk for incident prostate cancer because of preexisting prostatic intraepithelial neoplasia (PIN) did not show an increased risk of prostate cancer. There has been one small study examining the risk of TRT in men with high-grade PIN. These men should presumably be at higher risk for prostate cancer development. After a year of TRT, only one patient with previous high-grade PIN had a detected prostate cancer. The study included 70 men overall; 20 with high-grade PIN and 50 controls.[22] This study suggests that TRT does not significantly increase the risk of incident cancer even in an already high-risk population.

A landmark study by Marks *et al.*[23] suggested a possible explanation for the lack of association between TRT and an increased prostate cancer risk. In this double-blind, randomized, placebo-controlled trial, men with hypogonadism were given testosterone intramuscularly every two weeks for a total of six months. Intraprostatic levels of testosterone and DHT were obtained by prostate biopsy prior to initiation of TRT and after the six-month trial period. While levels of testosterone and DHT increased substantially in the serum, there was no change in the levels of these hormones by prostate biopsy. This finding would suggest that exogenous testosterone produces systemic effects without altering the intraprostatic androgen levels. Therefore, the androgen levels that could affect cancer risk (those within the prostate) remain unchanged.

In a series of compiled prospective studies of patients given TRT for up to three years, the rate of incident prostate cancer was 1.1%, a rate similar to that of the general male population.[2] Calof *et al.*,[24] performed a meta-analysis of 19 different trials of TRT in hypogonadal men. All 19 studies were prospective, double-blind, randomized, placebo-controlled trials of men 45 years of age or older. The analysis included a total of 643 men receiving TRT and 427 receiving placebos. There was no significant difference in incident prostate cancer between the men receiving TRT and those on placebo.

TESTOSTERONE REPLACEMENT FOLLOWING DEFINITIVE PROSTATE CANCER THERAPY

The use of TRT in men after definitive treatment for prostate cancer is still controversial. Definitive therapies include external beam radiation therapy (EBRT), brachytherapy (BT), or radical prostatectomy (RP). Some clinicians and investigators believe that a history of prostate cancer should be considered an absolute contraindication for TRT. Testosterone products contain package inserts stating that testosterone is contraindicated in men who have a history or prostate cancer or in men suspected of having prostate cancer.[25] Many urologists hesitate to use TRT in patients after RP. There is some concern that the rise in circulating androgen levels could promote recurrence of disease from residual tumor. Several different studies have evaluated this concern and investigated TRT use in men after RP. These studies have shown that TRT improves the symptoms of hypogonadism and increases circulating androgen levels without any suggestion of an increased risk of recurrence or persistence or prostate cancer.[26-28] Only one patient (1.4%) of the 74 reported in these studies had biochemical recurrence of prostate cancer. This patient had a Gleason score of 8, a known risk factor for biochemical recurrence after definitive therapy. Clinicians using TRT should exercise caution when considering TRT in patients with high-risk disease. Extraprostatic extension, positive margins, positive nodes, Gleason scores of 8 or more on biopsy, and invasion of the seminal vesicles are all considered to be high risks for biochemical recurrence. In patients with a high risk of recurrence, androgen deprivation has been previously demonstrated to improve survival.[29] Several studies with small populations and limited follow-up have been conducted of men given TRT after definitive therapy with either BT[30] or EBRT.[31] In the studies 31 patients with symptomatic hypogonadism and low testosterone levels received TRT for up to nine years. Of the men receiving TRT, 97% maintained testosterone levels below 0.5%. No failures were reported and the studies concluded that TRT might be safe in selected patients.

BENEFITS OF TESTOSTERONE REPLACEMENT

Observational evidence is accumulating to suggest that there is a relationship between normal serum testosterone levels and longevity, this effect is possibly due to the influence of androgens on lipids and cardiovascular risks. Shores *et al.*,[32] demonstrated a difference in survival between men with normal and low or borderline testosterone levels. Khaw *et al.*,[33] and Laughlin *et al.*,[34] both showed associations between testosterone levels and longevity. Khaw *et al.*, showed in a series of over 2,300 men, that the greatest longevity was in men with the highest levels of endogenous testosterone. Laughlin *et al.*, reported a 1.6-fold increase in the risk of death in men with the lowest

levels of endogenous testosterone. D'Amico *et al.,* studied the influence of androgen suppression therapy for prostate cancer on fatal myocardial infarction (MI). The study found that there is an earlier onset of fatal MI in men 65 years of age or older who have been on androgen suppression for six months or longer.[35] Although the previously mentioned studies demonstrated a relationship between androgen suppression therapy and cardiovascular risks, not all studies have shown the same relationship. In a study conducted by Bolla *et al.*,[36] the authors reported no increased risk of fatal cardiovascular events in men who received three years of androgen suppression after X-ray therapy. The study does not, however, address the question of the efficacy of radiation therapy plus or minus androgen suppression versus conservative management in men with T1c prostate cancer. In a separate trial including 206 men with unfavorable-risk, localized prostate cancer randomized to radiation therapy or radiation therapy plus six months of androgen suppression, fatal cardiovascular events occurred in 13 men in each treatment arm.[37] In men who received androgen suppression, the majority of fatal cardiovascular events occurred in those with moderate to severe co-morbidities (11 of the 13). This led to a loss of the survival benefit of androgen suppression in men with moderate or severe co-morbidities. Excess morbidity for men with lower testosterone was associated with cardiovascular risk, supporting the benefit of testosterone supplementation on cardiovascular risk factors. It has never been documented in randomized trials that TRT reduces the higher risk of fatal cardiovascular events in men with low endogenous testosterone production. In a recent update issued by the American Heart Association, American Urologic Association, and American Cancer Society, the authors indicated a relationship between the use of androgen suppression and fatal cardiovascular events.[38]

Hypogonadism is a major cause of secondary osteoporosis in men. Up to 20% of men with symptomatic, pathologic vertebral fractures and 50% of men with hip fractures are found to be hypogonadal.[39] In a study of 72 hypogonadal men, testosterone replacement was associated with an average 39% increase in bone density in the first year. Bone density eventually increased into the normal range and was maintained there throughout the study.[40]

Reduced testosterone levels are also associated with metabolic syndrome and Type 2 diabetes. Additionally, serum testosterone levels tend to be reduced in obese men. Decreased serum testosterone levels are now starting to be considered independent risk factors for metabolic diseases. A meta-analysis by Corona *et al.*,[41] reported that male hypogonadism is an independent risk factor associated with the metabolic syndrome. This meta-analysis also reported that men with hypogonadism and ED were more likely to have metabolic syndrome than men with hypogonadism without ED. This suggests that vascular atherosclerosis resulting from metabolic syndrome may be part of the pathophysiology of ED in men with hypogonadism. Additionally, there is evidence to suggest that men with ED and hypogonadism may derive mortality benefits from lifestyle modifications and pharmacologic interventions designed to reduce cardiovascular risk.[41] Studies of men undergoing androgen suppression for prostate cancer support the assertion that hypogonadism increases body fat and serum insulin and is associated with a high risk for developing diabetes. Testosterone replacement has been shown in clinical trials to decrease body fat and improve glycemic control and insulin resistance.[42] Testosterone replacement was associated with a decrease in mean glycosylated hemoglobin from 10.4% to 8.6%. Additionally, serum concentrations of free testosterone appear to be inversely correlated with the severity of carotid atherosclerosis in men with Type 2 diabetes.[43]

Previous guidelines[44,45] have suggested there is too little evidence in the literature regarding the safety of TRT in the setting of prostatic diseases including prostate cancer to make a definitive recommendation. The 2008 European Association of Urology (EAU) guidelines indicate that testosterone replacement can be used in men with symptomatic hypogonadism after successful treatment of prostate cancer provided that a prudent interval has passed with no evidence of recurrent disease.[46] The duration of a "prudent interval" is not specifically defined in the guidelines. Additionally, the guideline advises that a high risk of developing prostate cancer should be considered a contraindication for TRT. High risk for developing prostate cancer is not defined. As more information regarding the effects of TRT on the prostate and prostate cancer becomes available the risks and benefits of TRT can be more accurately assessed.

CONCLUSION

No clear relationship has been demonstrated between testosterone replacement and the risk of incident prostate cancer in any recent and carefully designed studies. There is no definitive evidence currently of any link between increased prostate cancer risk and short-term androgen replacement for symptomatic hypogonadism. Randomized trials studying TRT in men with a history of prostate cancer have not been conducted and comparative trials have shown no impact on prostate disease outcomes. There remains a need for long-term randomized trials to address the issue of TRT in men with a history of prostate cancer. There is no evidence of benefit from exogenous testosterone administration in men with normal endogenous testosterone levels. However, benefit has been shown with TRT in men who have symptomatic hypogonadism. Additionally, the potential role of TRT in reducing cardiovascular risks cannot be ignored. As with any form of therapy, clinicians should thoroughly discuss the anticipated risks and benefits of TRT before starting a patient on this treatment. Men

receiving TRT should continue to have regular PSA and DRE screenings and abnormalities should be evaluated. Provided that proper monitoring is carried out, TRT can be an appropriate and effective treatment for men with symptomatic hypogonadism.

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