Androgen Supplementation and Prostate Cancer Risk: Strategies for Pretherapy Assessment and Monitoring

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Since in men androgen levels decrease with age and result in symptoms of hypogonadism, the use of testosterone supplementation to treat symptoms resulting from hypogonadism is increasing. One potential complication of this treatment is the possibility of an increased risk of prostate cancer. Although most authorities agree that androgen is involved in the exacerbation of existing carcinoma of the prostate, the action of androgens on the carcinogenic process is not well understood. Attempts to demonstrate a correlation between hormone levels and prostate cancer have yielded inconsistent results. No clear evidence exists that androgen supplementation to restore physiologic levels produces any deleterious effects on the prostate. It is highly doubtful that when testosterone therapy is administered to middle-aged or older men, any potential prostate cancer promotion effect will be clinically manifested in the absence of already established cancer. It is, however, imperative that existing or developing prostate cancer be ruled out before initiation and during androgen replacement therapy. As with any therapeutic regimen, careful monitoring of the patient receiving treatment is recommended and constitutes good medical care.
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Testosterone levels decrease as men age. It is estimated that roughly one out of two men more than 50 years of age has free testosterone levels that are below those considered normal for younger men.[1] Testicular atrophy and decline in Leydig cell number lead to this decrease in serum testosterone.[2] Decline in androgen levels and resulting symptoms have been referred to as the male climacteric, andropause, and PADAM (partial androgen deficiency of the aging

male).[3] The symptoms of decreasing testosterone in the aging male are certainly less dramatic and occur over a longer time period than those of menopause in the female.[2] Men experience a continuous, slow decline in testosterone beginning in approximately the fourth decade of life.

The indication for testosterone therapy is hypogonadism resulting from deficiency of testosterone. Hypogonadism can be primary (testicular failure or resulting from testicular trauma), secondary (pituitary or hypothalamic failure), or sometimes both.[2] Common causes of hypogonadism are aging, obesity; severe systemic illness such as AIDS, uremia, and hepatic cirrhosis; and medications such as ketoconazole, glucocorticoids, spironolactone, lactone, cimetidine, phenytoin, and flutamide.[2]

Potential liabilities of androgen replacement in the hypogonadal male include polycythemia, gynecomastia, azoospermia, exacerbation of sleep apnea, and prostatic disease.[4,5] Possible prostatic complications include increase in lower urinary tract symptomatology caused by benign prostatic hyperplasia (BPH) or initiation or promotion of prostate carcinoma.

The Role of Androgens in Prostate Cancer Development

Prostate cancer remains a major health care concern. It represents the most common male malignancy and the second most common cause of cancer-related death.[6] Moreover, approximately 30% of men at postmortem examination have microscopic evidence of latent prostate cancer, and other autopsy studies have shown that the histological evidence of BPH is present in up to 90% of patients greater than 80 years of age and, of those, prostate cancer is present in greater than 50% of specimens that are well sectioned and reviewed.[7–10] We know that the development of BPH is a long process, with initiation beginning in men at approximately age 30.[8,11–12]

While we generally relate the male hormone, testosterone, to stimulation of the prostate, we know, more precisely, that the more active metabolite, dihydrotestosterone (DHT), actually stimulates prostatic tissue to a much greater degree.

Possible Mechanisms of Androgen Influence on Prostate Cancer Development

It is well established that circulating androgens are a central prerequisite for the growth of the normal prostate but the action of androgens on the process of carcinogenesis is not clear.

While we generally relate the male hormone, testosterone, to stimulation of the prostate, we know, more precisely, that the more active metabolite, dihydrotestosterone (DHT), actually stimulates prostatic tissue to a much greater degree. DHT forms through the reduction of testosterone by the enzyme 5-alpha-reductase.[13] As with testosterone, the role of DHT in the promotion of prostate cancer is not known. Both testosterone and DHT bind to the same androgen receptor protein, although DHT has a much higher binding affinity[14] and results in increased transcription.[7,15]

The factors associated with the progression of clinically latent carcinoma to the clinically recognized, aggressive phenotype are unknown.

Hormone Levels and Prostate Cancer: Is There a Correlation?

While circulating androgens are necessary for the development of prostate carcinoma, it has been well established that with advancing age, when the incidence of prostate cancer increases, serum testosterone levels decrease. Given that latent prostatic carcinoma develops many years before clinical diagnosis, this phenomenon may be of little significance.

Although a number of studies have looked at serum hormone levels in prostatic carcinoma, no pattern emerges. Indeed, as many studies have demonstrated increased testosterone levels in men with cancer as have demonstrated decreased levels.[17–25] However, a meta-analysis of studies examining prostate cancer incidence and serum levels of testosterone revealed a 2.34-fold increase in risk for prostate cancer in the men in the upper quartile of testosterone level relative to those in the lowest quartile.[26] Three studies failed to demonstrate a correlation between DHT level and prostate cancer.[22,22,25] Nomura and associates[27] demonstrated that serum dihydrotestosterone levels were lower and the testosterone/dihydrotestosterone ratios were higher in the prostate cancer cases compared with their controls. However, none of these associations or that of the other hormones was strongly significant. Barrett-Connor et al[17] found total testosterone, estrone, estradiol, and sex hormone-binding globulin were

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not related to prostate cancer, but showed a positive correlation between prostate cancer risk and serum androstenedione levels. Hsing and Comstock[28] demonstrated elevated luteinizing hormone (LH) and also confirmed Nomura's increased testosterone-to-DHT ratio in men with prostate cancer but did not show a correlation to testosterone or DHT. Due to the conflicting results of the studies, no conclusive evidence exists of a relationship between serum testosterone and prostate cancer.

Histological Reports

It would seem obvious to study hormone levels in the tissue of men with both BPH and prostatic carcinoma. However, numerous methodologic problems including delineation of actual histology of the tissue in question, variance in methods to determine hormone levels, and artifacts of tissue acquisition such as heat related to transurethral section have resulted in tremendous confusion in the reported studies.[29–32] The best study to date, reported by Walsh,[29] demonstrated there was no difference in tissue DHT levels between BPH and normal peripheral prostatic tissue. Geller and associates[33] report lower DHT values in men with untreated prostate cancer than in men with BPH.

Androgen Supplementation and PSA

The effect of hormonal regulation on prostatic tissue growth and function, particularly reflected by serum PSA level, is of course a well-studied area. Particular attention has been paid to the effect of androgen withdrawal as a treatment of prostatic carcinoma.

Several investigations have attempted to correlate serum PSA levels with testosterone levels.[34–40] Two studies, those of Behre and associates[40] and Svetec[35] demonstrated statistically significantly lower levels of PSA in hypogonadal men than normal men. Four other investigations[1,37,41,42] revealed a trend toward lower levels of PSA in hypogonadal men, although this trend did not achieve statistical significance in any of the studies.

It is highly doubtful that the administration of testosterone therapy produces any promotional effect in the absence of an already existing cancer.

Several investigators have measured PSA levels before and after testosterone replacement. In six reports[34–38,40] PSA was found to increase significantly after testosterone replacement. In others,[1,39,41–43] although there was a tendency for PSA to increase, this trend did not reach statistical significance. In only one study investigating this phenomenon, that of Snyder et al,[44] did the PSA level remain unchanged. Three investigators simply looked at the chance of PSA increasing to above the threshold of normal (4.0 ng/mL).[45–47] In none of these studies did this increase occur.

A number of animal models have demonstrated that exogenous androgens stimulate established prostate cancer in a dose-dependent fashion.[48,49] Testosterone given to patients with advanced metastatic prostate cancer results in severe pain at bony metastatic sites.[50] There have been three investigations in which supplemental testosterone was given to eugonadal men. Indications were obesity with low normal testosterone,[51] in healthy volunteers,[52] and in men in a long-term contraception trial.[43] In none of these investigations on eugonadal men was an increase in PSA observed. Again, due to the lack of agreement in the study results, no relationship between serum testosterone and PSA was established.

Studies which attempt to correlate increased testosterone with increased PSA levels have been unconvincing.

Cancer Risk and Patient Monitoring

Despite the conclusion that it is highly doubtful that the administration of testosterone therapy produces any promotional effect in the absence of an already existing cancer, the patient needs to be monitored. A standard urologic evaluation to rule out malignancy should be undertaken prior to initiating androgen supplementation. Recommendations include a carefully performed digital rectal examination (DRE) along with serum PSA measurements. If either the rectal examination is abnormal or the PSA level exceeds 4.0 ng/mL, ultrasound-guided prostate biopsy becomes mandatory. If the initial PSA levels are within normal limits and the DRE is negative, one should feel comfortable initiating androgen supplementation in properly identified patients. It is imperative that the patient be carefully monitored for any changes in these prostate risk findings and we would recommend reassessment at 3 months. At that time, if the PSA level exceeds 4.0 ng/mL, or there is a change in DRE, prostate biopsy is warranted. We recommend an additional prostate assessment in 3 more months (6 months after initiating therapy) and at least annually thereafter.

Conclusion

The effectiveness of testosterone therapy in ameliorating the signs and symptoms of hypogonadism in the aging male will lead to increased implementation of this therapy. There have been multiple attempts to correlate the administration of testosterone to prostate carcinogenesis, but the studies have failed to produce consistent results. Similarly, the studies which attempt to correlate increased testosterone with increased PSA levels have been unconvincing. Nor have the studies been able to link DHT, the more active metabolite of testosterone, to the development of carcinoma. The prevailing opinion is that restoring testosterone levels to physiologic levels offers no increased risk of carcinoma. However, there is little doubt that the studies show a deleterious effect on existing clinical carcinoma of the prostate. With the elimination of the presence of an existing carcinoma of the prostate, through physical examination and laboratory studies, before initiation of testosterone therapy, and the continuous monitoring of the patient throughout therapy, testosterone therapy will prove safe with regard to prostate health. ■

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Main Points

- Several studies have found a positive correlation between serum hormone levels and prostate cancer, whereas several other studies have failed to show this relationship.
- No clear evidence exists that adding supplemental androgen in the face of low testosterone levels is harmful.
- Patients need to be thoroughly evaluated to rule out prostate cancer before initiation of androgen supplementation and carefully monitored for malignancy and polycythemia once treatment begins.

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