

What is the risk of testosterone therapy after prostate cancer?

A. Morgentaler

A currently controversial topic is whether testosterone therapy may be safely provided to men after treatment for prostate cancer (PCa). For many decades, a prior history of PCa was considered an absolute contraindication for testosterone therapy, but recent evidence suggests that such treatment may not be as risky as once assumed. Indeed, using serum prostate specific antigen (PSA) as a biochemical marker, several small case series have reported no biochemical recurrences in men following radical prostatectomy or brachytherapy, and a recent case report noted a decline in PSA in a man with untreated PCa who received testosterone therapy for two years. The impetus for reconsidering testosterone therapy in these men stems from the growing recognition of the health benefits of testosterone therapy in hypogonadal men, including improvements in energy, vitality, sexual desire, erectile function, body composition, and bone mineral density (Chapter 37), as well as the desire of hypogonadal PCa survivors for an improved quality of life.

The origin of the historical prohibition against testosterone therapy in men with a history of PCa arose from the demonstration that PCa regressed with androgen deprivation and progressed with testosterone administration. Current evidence indicates that PCa is exquisitely sensitive to changes in serum testosterone at the extremely low end of the concentration range, but becomes indifferent to changes in serum testosterone at higher concentrations.

Testosterone therapy in men with a history of PCa

Three small case series have reported results of testosterone therapy after treatment for localized PCa. Results of testosterone therapy in a group of 7 men with undetectable PSA following radical prostatectomy revealed no recurrences, with follow-up as long as twelve years. In another study, no biochemical recurrences were observed in 10 men with undetectable PSA following radical prostatectomy. A third series reported no biochemical recurrences in 31 men treated with testosterone therapy for a median of 4.5 years following brachytherapy.

Of interest, a case report detailed a decline in PSA after two years of testosterone therapy in an 84-year-old hypogonadal man with untreated PCa. Pathology revealed a Gleason Score of 6 with cancer found bilaterally, in two

of six cores, but the patient declined treatment for his cancer. No clinical progression was noted despite a substantial increase in serum testosterone accompanied by improvement in clinical symptoms of hypogonadism.

Relationship of high serum testosterone and PCa

The prohibition against testosterone therapy in men with a history of PCa stems from the longstanding belief that higher testosterone would lead to more rapid PCa growth. A considerable amount of evidence suggests this belief is incorrect. A landmark study involving pooled data from 18 longitudinal studies failed to find any relationship between PCa risk and serum androgen concentrations in 3886 men with PCa and 6438 men without PCa who served as controls. Specifically, men with high serum testosterone were not at any greater risk of developing PCa than men with low serum testosterone. Moreover, a meta-analysis of placebo-controlled testosterone therapy studies revealed no increased rate of PCa or other adverse prostate events in testosterone-treated men versus placebo-treated men. Furthermore, no association has been shown between high testosterone concentrations and worrisome PCa features or outcomes, such as Gleason grade, stage at presentation, positive surgical margins, biochemical recurrence, or survival. Curiously, each of these has been reported in association with *low* serum testosterone.

Mechanism of action of androgens on prostate tissue

There are at least two likely mechanisms contributing to the androgen-indifference of PCa beyond near-castrate testosterone concentrations. One is that the androgen receptor (AR) has a finite binding capacity for androgen, with maximal binding (saturation) occurring at low androgen concentrations, approximately 4 nM (120 ng/dl). A second is the demonstration that intra-prostatic concentrations of testosterone and dihydrotestosterone appeared unchanged after 6 months of testosterone administration despite large increases in serum testosterone, suggesting that the intra-prostatic hormonal milieu may be relatively protected from changes in serum. The saturation model is supported by multiple studies in animal models, prostate cancer cell lines, and humans. For instance, castrated animals exposed to varying concentrations of serum testosterone demonstrate a steep androgen-dependent prostate growth curve, but then reach a plateau at which increasing testosterone concentrations result in no further prostate growth. Similar results are seen in the androgen-sensitive LnCaP cell line, with even log increases in testosterone or DHT producing no greater rate of cell division once a plateau

has been reached. In healthy men, no significant changes in PSA or prostate volume were noted with exposure to supraphysiologic testosterone concentrations for up to 40 weeks. These results indicate that there is a limit to the ability of androgens to stimulate prostate growth.

Discussion

Although controlled studies of testosterone therapy in men with PCa are lacking, the limited available evidence suggests that such treatment may not pose undue risks. The historical prohibition against this treatment has been based on an assumption that PCa is sensitive to changes in serum testosterone throughout the range of testosterone concentrations, whereas current evidence suggests that the androgen sensitivity of PCa is limited to the extremely low range of serum testosterone concentrations, and becomes androgen-indifferent at concentrations typically seen in hypogonadal and eugonadal men.

Further studies are clearly needed to provide a definitive assessment of safety and risk with testosterone therapy in men who have undergone treatment for PCa. It is important to recognize the possibility that such studies may even demonstrate a *beneficial* impact of testosterone therapy on PCa outcomes, based on the association of worrisome PCa features with low serum testosterone, and experimental evidence that androgens may inhibit prostate proliferation and promote a more differentiated and less invasive phenotype. In the meantime, it is recommended that clinicians who wish to offer testosterone therapy to men with a prior history of PCa should discuss the fact that safety data are lacking, and document informed consent.

Suggested reading

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