Testosterone replacement therapy after prostate cancer

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Recent evidence suggests that testosterone replacement therapy after prostate cancer treatment may be safer than previously thought. The authors review the basis for the common dilemma as to how to approach the treatment of testosterone deficiency after successful treatment for prostate cancer, and explain how the paradigm is shifting as our knowledge of androgen physiology grows.

Testosterone deficiency syndrome (TDS) is a common condition characterised by serum androgen deficiency that adversely affects the function of multiple organ systems and negatively impacts on the quality of life of ageing men. The clinical symptoms include sexual dysfunction such as erectile dysfunction and decreased libido, as well as fatigue, depressed mood, impaired cognition and decreased muscle mass (Figure 1).[1] The incidence of TDS is almost half a million new cases per year in men in their fifth, sixth and seventh decades of life, and as a result of the expanding population of the elderly, the incidence of TDS is on the rise.[2]

Although most cases of TDS occur in ageing men, for which the syndrome is commonly referred to as late-onset hypogonadism or andropause, TDS can also occur in younger men. Treatment of TDS with testosterone replacement therapy (TRT) is appropriate when the total testosterone level is below the lower limit of normal, generally accepted to be 300ng/dl (10.4nmol/l).[3]

TREATMENT DILEMMA

Prostate cancer is the most commonly diagnosed visceral malignancy in American men, and the lifetime risk of developing prostate cancer is 15.4 per cent for whites and 18.3 per cent for African Americans.[4] A common dilemma now facing both urologists and primary care doctors is how to approach the treatment of TDS after prostate cancer.

Huggins and Hodges' Nobel Prize-winning work published in 1941 concluded that 'higher serum testosterone leads to increased prostate cancer risk and invariably stimulates prostate cancer growth'.[5] Their paper has provided the foundation for a long-standing belief lasting over half a century that TRT in

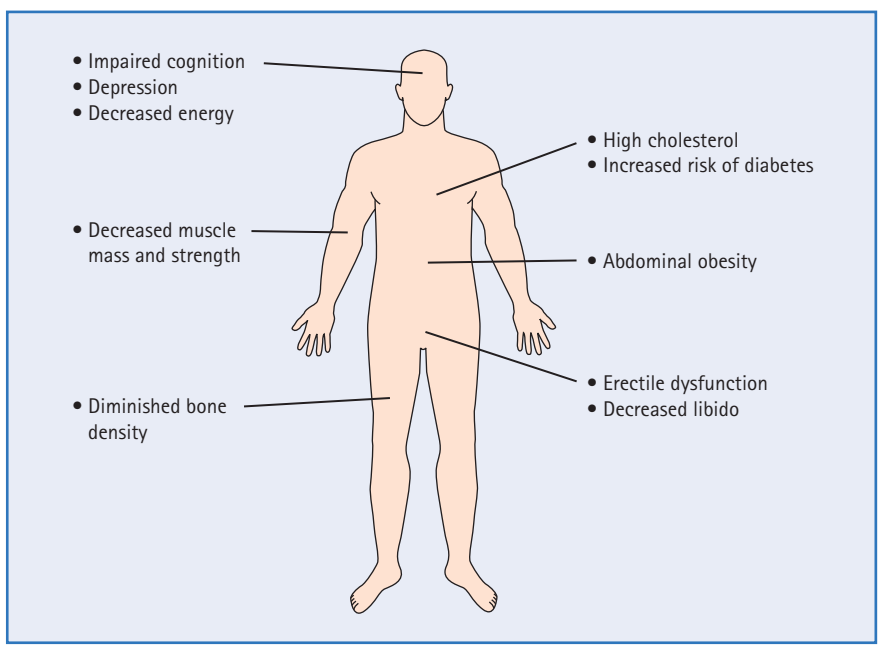

Figure 1. Multi-organ effects of testosterone deficiency syndrome

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a man with a history of prostate cancer could exacerbate his disease. Indeed, the most effective treatment of metastatic prostate cancer is androgen deprivation; however, the reverse may not be true.

The paucity of clear evidence-based data, along with the difficult task of debunking an age-old theory, creates a treatment dilemma for how to approach the symptomatic hypogonadal patient after successful prostate cancer treatment. Normalisation of testosterone clearly has beneficial effects on the quality of life of the ageing male, and recent evidence suggests that TRT after prostate cancer treatment may be safer than previously thought. There are now several case series totalling almost 150 men treated with prostatectomy, brachytherapy and external beam radiation who have been safely treated with testosterone replacement, and the paradigm is shifting as our knowledge of androgen physiology grows.[6–11]

The current understanding of testosterone physiology indicates that prostate cancer does not have an increased growth rate with testosterone levels in the normal physiological range. A recently re-evaluated saturation model of androgen to androgen receptor binding sites theoretically explains how the change in prostate cancer growth rate occurs only at or below the castrate level of serum testosterone. There is also new evidence that, compared with higher testosterone levels, hypogonadism is actually of more significant concern secondary to its association with worrisome features of prostate cancer.

No randomised controlled trials are available to date, although the latest available data support TRT after prostate cancer treatment as a safe treatment, with minimal to no risk of prostate cancer recurrence or progression.

DEVELOPMENT OF PROSTATE CANCER DURING TRT

The safety and efficacy of testosterone replacement for hypogonadal men has been studied, and several recent publications have reported that the prostate-specific antigen (PSA) level changes observed over time in these men are minimal, and the development of prostate cancer during treatment is rare. Several studies have shown a small initial increase in PSA levels after beginning TRT, which stabilises over time.[12–14] In a meta-analysis of 19 randomised, placebo-controlled TRT studies of 651 men, there were no greater rates of prostate cancer, elevated PSA, or prostate biopsies in men treated with testosterone versus placebo.[15]

To evaluate the development of prostate cancer during TRT, our group at the University of North Carolina retrospectively reviewed 81 hypogonadal men treated with testosterone for a mean of 34 months. Four men (5 per cent) developed prostate cancer after a mean 33 months of TRT. All of these malignancies were successfully treated. Of the 95 per cent of men who did not develop prostate cancer, the PSA did not change significantly at one-year intervals for a total of five years (Figure 2). We concluded that the incidence of prostate cancer in our cohort of hypogonadal men taking TRT was no greater than that in the general population, and prostate cancer can be effectively diagnosed and treated in men taking testosterone.[16]

TRT AFTER SUCCESSFUL PROSTATE CANCER TREATMENT

There are now several case series totalling almost 150 men treated with radical prostatectomy, brachytherapy and external beam radiation who have been safely treated with TRT. Khera and colleagues followed 57 hypogonadal men who initiated TRT a mean 36 months after radical prostatectomy. Over a follow-up period of 13 months, there were no PSA recurrences.[6]

In a study of seven men with undetectable PSA after radical prostatectomy who were treated with TRT, no recurrences were noted with follow-up as long as 12 years.[7] In another study of 10 hypogonadal men with undetectable PSA after radical prostatectomy, there were no biochemical recurrences during TRT.[8] There was a single biochemical recurrence after radical prostatectomy one year after initiating TRT in a man with a Gleason score of 8.[9] In a series of 20 men who underwent either radical prostatectomy or external beam radiation, there was a single recurrence.[10]

In 31 men undergoing TRT after brachytherapy for prostate cancer treatment, PSA levels were <1.0ng/ml in all the men and <0.1ng/ml in 74 per cent of the men at a median follow-up of 4.5 years.[11]

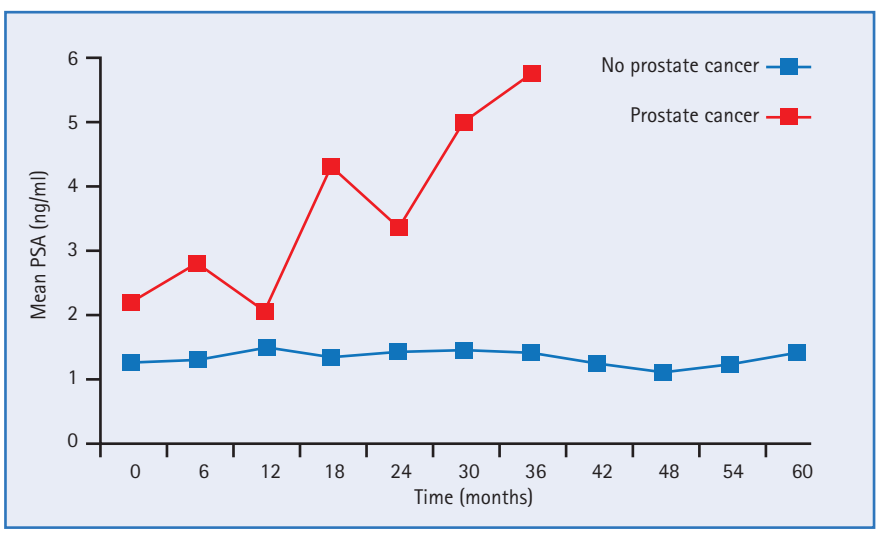

Figure 2. Change in mean prostate-specific antigen (PSA) with time in hypogonadal men on testosterone replacement therapy with or without prostate cancer[16]

In total, of men with prostate cancer successfully treated with radical prostatectomy, brachytherapy or external beam radiation who later underwent treatment with TRT, biochemical recurrence occurred in two of 147 men (1.4 per cent).

THE SATURATION THEORY AND THE BASIS FOR SAFETY

While androgen deprivation therapy is the gold-standard treatment for metastatic prostate cancer, leading to rapid decreases in PSA and cancer regression, the converse theory proposed by Huggins and Hodges that androgens stimulate prostate cancer growth in a direct relationship may not be true. To better explain this phenomenon, the saturation model of testosterone's effect on prostate cancer growth was recently re-evaluated.[17]

After an exhaustive review of all available studies investigating the prostatic effects of manipulation of androgen concentrations, the proposed saturation model is based on biochemical limits of androgen to androgen receptor binding sites. The model states that prostate cancer growth is exquisitely sensitive to variation in serum testosterone levels below castrate range based on available androgen binding sites, but that above the castrate range, prostate cancer growth is insensitive to testosterone variations (Figure 3).

Clinically, recent studies support the saturation model; that is, eugonadal testosterone levels, whether physiological or pharmacologically replaced, do not appear to promote prostate cancer growth. Although large PSA changes occur in both malignant and benign prostate tissue after androgen deprivation, natural testosterone variations do not affect PSA, even when it has been studied at supraphysiological concentrations.[18,19]

HYPOGONADISM AND WORRISOME PROSTATE CANCER FEATURES

A relationship between high or normal serum testosterone levels and worrisome features or outcomes of prostate cancer has never been identified. On the contrary, there is evidence that low testosterone may be associated with both prostate cancer and higher grade disease.

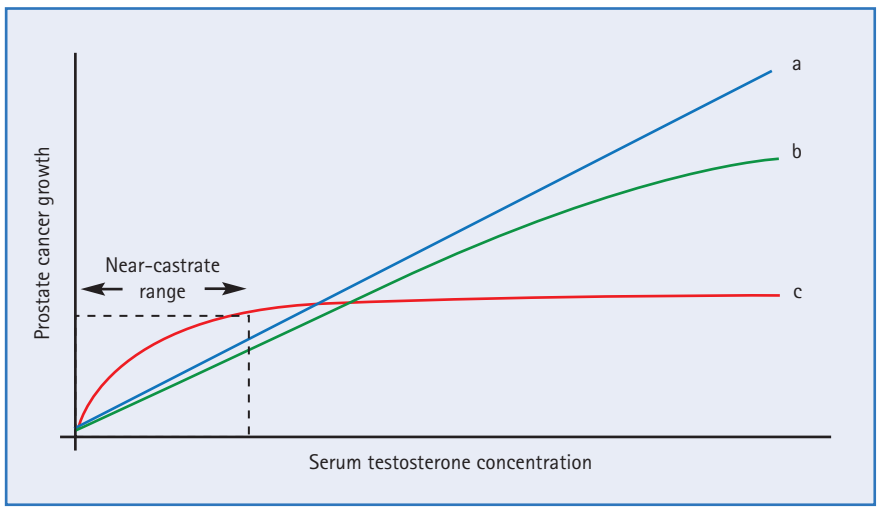

Figure 3. The traditional model of testosterone-dependent prostate cancer growth suggested that greater serum testosterone concentrations would lead to greater cancer growth (curves a and b). The saturation model (curve c) describes a steep testosterone-dependent curve at testosterone levels at or below the near-castrate range, with a plateau representing little or no further growth above this concentration. Redrawn from Morgentaler and Traish,[17] with permission

Yamamoto and colleagues studied the association of hypogonadism and PSA failure after treatment with radical prostatectomy by examining preoperative testosterone levels. Of 272 men, 49 were hypogonadal preoperatively, and the risk of PSA failure at five years was 2.7-fold higher for the hypogonadal men compared with the eugonadal men.[20]

In a study of 460 men with diagnosed prostate cancer, preoperative hypogonadism was associated with high Gleason score.[21] Morgentaler and Rhoden reported a series of 345 hypogonadal men with PSA <4.0ng/ml who underwent prostate biopsy. The overall cancer rate was 15 per cent, but the risk of a positive biopsy increased as the testosterone level decreased. Prostate cancer was detected in 21 per cent of men with a testosterone level <250ng/dl, and in only 12 per cent of men with a testosterone level >250ng/dl (p<0.05). The combination of a PSA >2.0ng/ml and hypogonadism was particularly worrisome, with a cancer rate of over 30 per cent.[22]

CONCLUSION

The current data, albeit none from randomised controlled trials, appear to disprove the theory that there is a direct relationship between testosterone and the growth of prostate cancer. Rather, the most plausible explanation for what is seen clinically in the current era of TRT is supported by the recently re-evaluated saturation model, which states that, secondary to limited androgen receptor binding sites, prostate cancer growth is sensitive to variations in serum testosterone levels only below castrate range.[17]

Based on all available data, as well as our personal experience, it is our opinion that TDS can be safely treated with TRT after successful prostate cancer treatment. The timing of TRT certainly needs evidence-based data, but we generally wait at least six months after prostate cancer has been treated before initiating therapy. Frank discussions with the patient often provide the best roadmap for the timing of therapy.

We are still a long way from an official statement of safety by the US Federal Drug Administration, the American Urological Association, or the European Association of Urology, but as more data are published we look forward to the reassurance of our current clinical practice.

Declaration of interests: *none*

KEY POINTS

- **Testosterone deficiency syndrome (TDS) is a common condition that adversely affects the function of multiple organ systems and negatively impacts on the quality of life of ageing men**
- **Although most cases of TDS occur in ageing men (late-onset hypogonadism or andropause), it can also occur in younger men**
- **There has been a long-standing belief that testosterone replacement therapy in a man with a history of prostate cancer could exacerbate his disease**
- **However, there is now evidence that testosterone replacement is safe in men who have been successfully treated for prostate cancer**
- **There is also evidence that, compared with higher testosterone levels, hypogonadism is of more significant concern secondary to its association with worrisome features of prostate cancer**

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