Review Article

Challenges to treat hypogonadism in prostate cancer patients: implications for endocrinologists, urologists and radiotherapists

Giovanni L. Gravina[1,2,3], Stefania Di Sante[2], Erika Limoncin[1], Daniele Mollaioli[1], Giacomo Ciocca[1], Eleonora Carosa[1], Patrizia Sanità[1], Ernesto Di Cesare[3], Andrea Lenzi[2], Emmanuele A. Jannini[4]

[1]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy; [2]Department of Experimental Medicine, Sapienza University of Rome, Roma, Italy; [3]Department of Biotechnological and Applied Clinical Sciences, Division of Radiotherapy, Laboratory of Radiobiology, University of L'Aquila, L'Aquila, Italy; [4]Department of Systems Medicine, Tor Vergata University of Rome, 00131 Roma, Italy
Correspondence to: Emmanuele A. Jannini, MD. Department of Systems Medicine, Tor Vergata University of Rome, Via Montpellier 1, 00131 Roma, Italy. Email: eajannini@gmail.com.

Abstract: The literature suggests that the serum testosterone level required for maximum androgen receptor (AR) binding may be in the range of nanomolar and above this range of concentrations; this sexual hormone may not significantly affect tumour biology. This assumption is supported by clinical studies showing that cell proliferation markers did not change when serum T levels increased after exogenous T treatment in comparison to subjects treated with placebo. However, a considerable part of the global scientific community remains sceptical regarding the use of testosterone replacement therapy (TRT) in men suffering from hypogonadism and prostate cancer (Pca). The negative attitudes with respect to testosterone supplementation in men with hypogonadism and Pca may be justified by the relatively low number of clinical and preclinical studies that specifically dealt with how androgens affect Pca biology. More controversial still is the use of TRT in men in active surveillance or at intermediate or high risk of recurrence and treated by curative radiotherapy. In these clinical scenarios, clinicians should be aware that safety data regarding TRT are scanty limiting our ability to draw definitive conclusions on this important topic. In this review we critically discuss the newest scientific evidence concerning the new challenges in the treatment of men with hypogonadal condition and Pca providing new insights in the pharmacological and psychological approaches.

Keywords: Hypogonadism; prostate cancer (Pca); psychotherapy; radiotherapy; testosterone; treatment

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Introduction

Up to 25% of older men experience hypogonadism, and the prevalence is higher in men with comorbid disease (1-5). Hypogonadal men have low serum testosterone levels and symptoms of androgen deficiency, including a decrease in energy and libido, muscle mass and bone density, as well as impairment in cognition and sexual function, and depressive symptoms (6). During the past decade, there has been increasing awareness of the health benefits conferred by testosterone replacement therapy (TRT). TRT for hypogonadism increases muscle mass and bone mineral density, decreases fat mass, and improves mood, libido, and sexual performance (7). However, TRT may not be appropriate for all men. The most important and controversial implications are with regard to the use of testosterone therapy in men with symptomatic testosterone deficiency and a history of prostate cancer (Pca). There is an historical fear that administration of exogenous testosterone may increase risk of developing Pca or an aggressive form of the disease. Pca was explained by what was called the androgen hypothesis: (I) androgens play a key role in the etiology of Pca, (II) high testosterone is a risk factor for Pca, (III) low levels of testosterone are

protective, and (V) administering testosterone to men with existing Pca universally causes rapid growth—something every trainee at that time learned was like "pouring gasoline on a fire", or "feeding a hungry tumor". Although the dramatic effects of androgen deprivation therapy in Pca are indisputable, current evidence fails to support the concept that increasingly high serum testosterone leads to ever-greater growth of benign or malignant prostate tissue (8).

Testosterone levels as a risk determinant for Pca

It is a common belief that that higher testosterone levels are associated with increased probability of developing Pca whereas lower levels of this sexual hormone should be associated with a lower risk of developing Pca. A growing body of evidence suggests that this is a false myth since lower testosterone levels have been associated with a greater risk of developing PCa. Additionally lower testosterone levels are a negative pathologic predictor of poor outcomes in men suffering from Pca. A recent study on men with Pca, García-Cruz and co-workers found that testosterone level was inversely related the percentage of tumor in the biopsy and that lower testosterone levels were related to a higher risk of Pca progression (9). In patients treated by radical prostatectomy (RP) and low testosterone levels a significantly higher incidence of extra-prostatic invasion and biochemical recurrence were observed (10).

A logical question would be whether it is the low testosterone that increases the risk of Pca or if it is the Pca that increases the risk of having low testosterone. In this regard literature seems to support the latter. Significant increases in serum testosterone levels and gonadotropins have been reported after RP even in the absence of androgen deprivation (ADT). Authors found that one year after RP, a significant increase in luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels was observed with a significant increase in the serum testosterone levels. Interestingly, men with higher Gleason score (7 to 10) had lower serum testosterone levels at baseline with respect to men with Gleason score 2 to 6. These data seem to suggest that may be a significant impact of high grade Pca on the hypothalamic-pituitary axis. Other authors also found that Pca exerts an inhibitory effect on testosterone synthesis, with a significant increase in testosterone, LH, and FSH one yr. ehen tumor is removed by RP (11). Finally, a cross-sectional study of 55 men with localized Pca (12) showed an increase in the serum levels of LH, FSH and dihydrotestosterone (DHT) of 53%, 21% and 13%, respectively with no significant changes in any other serum hormone investigated.

TRT in men treated by RP

A study population of 3,886 men with Pca and 6,438 age-matched controls, found no relationship between Pca risk and serum concentrations of testosterone, DHT, or free testosterone (13).

Muller *et al*. reported on 3,255 men in the placebo arm of the reduction by Dutasteride of Pca Events (REDUCE) trial who underwent planned prostate biopsies at 2 and 4 years. and found that baseline serum testosterone and DHT levels were unrelated to Pca detection or grade (14).

No prospective, controlled studies have yet been performed with adequate population sizes and duration to definitively assess Pca risk with testosterone therapy, but evidence to date fails to suggest increased risk. A meta-analysis of 19 placebo-controlled testosterone therapy cases found no significant increase in Pca or development of prostate specific antigen (PSA) >4.0 ng/mL in men treated with testosterone therapy versus placebo (15). Shabsigh *et al*. conducted a systematic review of 11 placebo-controlled studies and found that men who received testosterone therapy had neither increased Pca risk nor greater Gleason grade among those who developed Pca (16).

Several investigators have reported the use of testosterone therapy in men after curative treatment for Pca.

Kaufman reported no biochemical or clinical evidence of cancer recurrence in seven men who received testosterone therapy after prostatectomy, with the longest follow-up 12 years (17).

Agarwal *et al*. reported , no cancer recurrences in ten hypogonadal patients with organ confined Pca treated with prostatectomy and testosterone therapy (18). Khera *et al.* found that TRT is effective in improving testosterone levels, without increasing PSA values, in 57 hypogonadal men who have undergone prostatectomy (19).

Pastuszak *et al*. performed a review of 103 hypogonadal men with Pca treated with testosterone after prostatectomy (treatment group) and 49 non hypogonadal men with cancer treated with prostatectomy (reference group). There were 77 men with low/intermediate (non-high) risk cancer and 26 with high risk cancer included in the analysis. All men were treated with transdermal testosterone, and evaluated for more than 36 months. Median follow up was 27.5 months, at which time a significant increase in testosterone was observed in the treatment group. A significant increase in

prostate specific antigen was observed in the high risk and non-high risk treatment groups with no increase in the reference group. Overall 4 and 8 cases of cancer recurrence were observed in treatment and reference groups, respectively. Although this preliminary data may suggest that testosterone therapy may not harm or eventually protect against Pca development or recurrence (20), the limited number of studied patients and the absence of a randomization design do not allow us to generalize these conclusions to all patients.

These studies confirm the new concept that testosterone therapy may actually protect against Pca development or recurrence. Also, emerging data demonstrating that androgens promote less aggressive phenotypes and inhibit dedifferentiation in some Pca cell lines (21,22).

Indeed, in a recent publication, San Francisco *et al*. reported that low levels of free testosterone represented a significant risk factor for Pca disease reclassification (progression) in men undergoing active surveillance (23).

However, it should be recognized that the number of reported cases is still small and heterogeneous. There is clearly the need to design and conduct randomized trials for assessing the impact of TRT on Pca since the current recommendations, which suggests to limit TRT to symptomatic hypogonadal men successfully treated for Pca after a prudent interval, derived from retrospective analyses. The timing of T therapy initiation remains undefined. For men who underwent RP the "prudent interval" is achieved once the PSA is no longer detectable. The situation is less simple for men who received radiotherapy since undetectable levels might not ever be achieved (7).

TRT in men treated by curative radiation therapy (RT)

Treating hypogonadal men by TRT after RT can pose specific and potentially serious problems. A well-known phenomenon happening in subjects treated by RT is that PSA levels, after this treatment, do not become undetectable and a transient increase in the PSA values after nadir achievement can cause confusion regarding recurrence versus other benign causes. Additionally, short- and long-term ADT by LH-RH analogues is considered a standard of care in association with RT in intermediate and high-risk Pca improving Pca specific mortality and overall survival (24,25). The Baylor group retrospectively reviewed their data on hypogonadal men (13 patients) receiving TRT after treatment with either brachytherapy or external beam radiotherapy (EBRT) (20). Four patients fall into a very low or low risk for recurrence, seven in the intermediate risk, and two in high risk, respectively. Four patients received ADT with RT, and three of them also received TRT, which was held during treatment. No significant changes in PSA were noted during 67.3 months (median 2.5 yrs) of follow-up. Although the small sample size and the short follow-up, the authors suggested the use of TRT in hypogonadal men treated with curative RT. Sarosdy analyzed 31 patients treated with brachytherapy and followed for a mean of 60 months (26). Three patients received combined EBRT and brachytherapy with 14 patients also receiving concomitant ADT. Interestingly, one patient experienced a rise in PSA after TRT, which steadily declined thereafter, and only one patient with 5-year post-brachytherapy has a PSA greater than 0.5 ng/dL. In no patients documented recurrence, or progression of disease and for this reason, no men stopped TRT. Morales treated five hypogonadal men with TRT once the PSA nadir was reached after EBRT, and none had evidence of recurrence based on PSA or digital rectal exam (DRE) (27). Davila and co-workers reviewed six men treated with EBRT for Pca and treated with TRT. None of whom developed biochemical recurrence although the follow-up was of only 9 months after radiation course (28).

While we have yet to see the randomized trial that will answer the question of risk associated with TRT in men Pca and treated by RT, there are interesting data that suggest as men with very low or low risk Pca according to National Comprehensive Cancer Network (NCCN) guidelines may be considered eligible for a treatment with TRT when clinically indicate. For patients with intermediate or high risk for recurrence who reach castration range during treatment with short- and long-term ADT, particular caution must be used. In fact, according with the saturation model, Pca is sensitive to T levels only in the castrate range, above which androgen receptors (ARs) are saturated and more T does not produce more growth (29). The picture is more clear in patients treated with RP, as any PSA elevation thereafter is concerning for disease recurrence. Some authors suggest that TRT may be optimal for men with "no residual disease," which may be defined for patient treated with RP as a PSA <0.2 and <2 ng/mL for the post-radiation population (30).

Morgentaler and co-workers studied a cohort of men with untreated Pca and treated with RTR for hypogonadal condition (31). Thirteen with these clinical characteristics received TRT for a median of 2.5 yrs. Gleason score at biopsy ranged from 6 to 7 in the 13 studied subjects. During

TRT mean serum testosterone concentration increased from 238 to 664 ng/dL and mean PSA as well as prostate volume did not significantly change. On re-biopsy, in 54% of subjects no evidence of Pca was observed, while two subjects experienced an upgrading of pathologic stage with no change in the oncological parameters during follow-up. No local progression or distant disease was observed in this study. Morales studied seven hypogonadal patients with untreated and treated Pca (32). Clinical criteria to stop TRT were (I) an increase in PSA level >1 ng/mL quarterly or (II) a PSA doubling time less than 12 months. After discontinuing TRT, a return to pretreatment PSA levels was an indication to reinitiate TRT. Four patients demonstrated unpredictable increases in PSA level, occurring immediately or as late as after 36 months after starting TRT. One patient with a rising PSA later underwent RP. In one patient, intermittent TRT resulted in synchronous changes in PSA levels.

Clinical experience with testosterone in men with castration resistant Pca

A body of biological and clinical evidence suggests that pulsed T treatment may have a positive impact on the biology of Pca. In this regard, an anti-proliferative effect from immediate T boosts within the physiological range was observed in androgen-sensitive Pca cells by other authors (33-35). Brendler at the Brady Urological Institute (36) used parenteral testosterone in a number of men with CRPC. He found a clinically significant improvement in several measurable parameters which included decreased pain, decreased prostate size and decreases in acid and alkaline phosphatase. Similarly, Prout and Brewer (37) administered parenteral testosterone in men who were either hormonal naive or recently or long-term castrates. In the long-term castrate group four of five men treated with testosterone for at least one month experienced clinical benefit. Of note, one man in this group with severe back pain, weakness and anorexia had a 10-month response with complete cessation of pain and decrease in acid phosphatase. On the contrary the five remaining patients received testosterone for less than 19 days and experienced tumor progression. More recently, Mathew (38) reported a case report on the use of testosterone gel replacement therapy in a man with castration-resistant prostate cancer (CRPC) and observed a sustained decrease in PSA that lasted for approximately one yr. Recently, two Phase I studies reported the results of the use of testosterone gel in men with CRPC. In the first study, Szmulewitz selected 15 men with rising PSA and minimal bone disease. He evaluated the effect of increasing doses of transdermal testosterone in this cohort of men with early CRPC (39). Groups of five men were treated with 2.5, 5.0, or 7.5 mg/day of transdermal testosterone reaching a serum concentrations T of 305, 308, and 297 ng/dL, respectively. In this study only one patient had symptomatic progression whereas three patients had a decrease in PSA and men treated at the highest dose had a prolonged time to progression. No significant toxicity was observed in the studied cohort except one man who experienced grade 4 cardiac toxicity 53 weeks after T therapy. In the second study, Morris evaluated the effect of transdermal testosterone at a dose of 7.5 mg/day administered for 1 week, 1 month or until disease progression in small cohort of 12 patients with CRPC (40). They observed no grade 3 or 4 toxicities and no pain flares. Average serum testosterone levels were within normal limits and no objective responses were observed. Four patients had declines of PSA of at least 20% and 1 patient out of 12 achieved a >50% decline in PSA. These clinical results from a limited case series or case reports seem to suggest that systemic testosterone can be administered to men with CRPC and minimal disease burden. However no evidence exists that more advanced CRPC disease may respond to testosterone treatment as hormone sensitive Pca in early stage. Additionally no practical indications may be derived from this limited number of clinical evidence. A very comprehensive explanation of molecular events leading to tumour cell growth inhibition under rapid cycling of physiologic or supra-physiologic T boost may be explained by studies defining bipolar androgen therapy (BAT) (33-35). AR may function as a licensing factor for DNA replication, which may be important for the proliferation properties of Pca tumour cells (34). In this regard, without a timely and complete AR degradation during mitosis, the origin of DNA replication remains AR-bound stalling, in this way, the re-licensing for the subsequent cell cycle. Therefore, it seems clear that T level is a critical event in determining AR degradation. Rapid concentration changes obtained under both physiological and supra-physiological T supplementation may prevent AR degradation during mitosis, thus stabilising this receptor and resulting in G1/S-phase growth arrest (34,41).

Testosterone as protective biological determinant against the development or recurrent Pca

Although a low number of studies have investigated

men receiving TRT after RP, there is a lower rate of Pca recurrence and progression in this cohort of patients compared to subjects not receiving TRT after RP. Although most patients with Pca treated with surgical and non-surgical treatment with curative intent may be considered oncologically cured, around 15% to 40% will experience a biochemical-recurrence (42). Interestingly the recurrence rates of subjects being treated with TRT after RP seems to be even lower than found in men a low risk of recurrence and not treated with TRT (21). The explanation of this paradox was explained by Sonnenschein who evaluated the biological response of LNCaP tumor cells to different concentrations of androgens (43). The evidence derived from this study seems to suggest that the proliferative response in this cellular model may be not directly mediated by intracellular ARs and those androgens were able to trigger an inhibition of cell proliferation at higher concentrations. Other authors suggested that testosterone may have a beneficial effect on Pca by promoting the insurgence of a less aggressive phenotype (44).

New frontiers of Psychotherapy in men with hypogonadism and Pca

Most of the men live the experience of diagnosis and treatment of Pca with high levels of stress in all aspects of life.

Specifically, the diagnosis may prefigure itself not only as a threat to survival, but also to prospects for future well-being of the patient in several ways: from the physical to the social, from the familiar to the sexual.

In fact, although many men often deal with great courage this experience, some have high levels of psychological and sexological stress (45,46).

On an equal age, men with Pca have a higher probability of having erectile dysfunction (ED) of 10-15 times (47). Other distressing effects associated with the treatment include shortening of the penis (68%), loss of sexual desire (60-80%), orgasms unsatisfactory (64-87%), sexual dissatisfaction overall (61-91%) (48,49). These effects may lead to altered sexual performance; changes in relationships with partners; progressive reduction in sexual fantasies and in self-esteem (49,50).

In addition, many men are hesitant to seek help from a sexual health expert (49). This is particularly problematic for men who have undergone RP, where a rapid return to sexual activity (3 months after the surgery), associated with couple therapy, may increase the recovery rate of spontaneous erections and improve responses to treatment for ED (51).

However, existing medical and support services are geared exclusively towards the patient, not paying enough attention to the couple's relationship and ignoring the needs of the partner, who are less likely to consider their sexual needs and more focused on the physical and psychological recovery of their man (52,53).

The psychological distress of female partners may increase if they have a limited knowledge about the post-operative course and treatment modalities.

In addition, female partners may be reluctant to share their discomfort with their partners, avoiding to adding new stress to the couple; This is even more likely when the discomfort regards the sexuality (52). This lack of communication leads the partner to live on their own and with limited tools anguish and anxiety derived from the male oncological pathology (54). The discomfort experienced by women is also aggravated by the demands of emotional support from their partners, which leads to having to manage not only their own anxiety, but also the anguish of their husbands (52,55).

Patients and partner capacity to deal with Pca and subsequent treatment side effects are correlated (56) and may have a negative impact on the marital relationship (57). The reactions of the partner to sexual dysfunction and the support they provide seem to influence the level of acceptance of sexual changes experienced by humans (58). In addition, the ability of the female partner's pleasure during sexual activity (in the absence of overt dysfunction) is a strong predictor of improved sexual satisfaction in the male partner (49).

This leads to the need to provide targeted support to couples that promotes communication and adaptation to sexuality post-cancer. This strategy, for example, has led to excellent results in couples with women suffering from breast or gynaecological cancer and will promote communication strategies that included the topic of cancer (59).

In contrast to women, men are less likely to seek psychological help and are reluctant to use sexual aids effective after treatment of Pca, despite the high levels of sexual dissatisfaction with the results of treatment. The lack of engagement with psychosocial support programs after Pca has been described in connection to a conflict with the values that underpin masculine identities (60).

Effective support interventions need to use delivery methods and sources that are acceptable for this group of patients. Men prefer individual consultations to support sexuality after Pca (61). Specifically, the interventions most

accepted are Internet-based (62,63) and self-help groups, where discussions among peers provide emotional support and information, reducing the feeling of social isolation (64). A feasibility study of a program of support among patients with Pca reported a decrease of depressive symptoms and a better self-efficacy in the short term, with people who speak more frequently about incontinence, ED and prostate-specific antigen test (65). In addition, a randomized controlled trial of a training program group focused on treatments for Pca (66), found that only with the addition of Peer discussion to the provision of information by an expert allow a better understanding and internalization of information, compared to a control group. An advantage of peer supportprovided by the patients veterans is that it is inexpensive compared to approaches provided by professional nurses.

Although this approach is very promising, currently there are no randomized controlled trials to evaluate the effectiveness of peer support in the reduction of psychological distress and sexual. However, the reduction of the costs of peer support than professional approaches, although not yet quantified, makes this a potentially lucrative source of support. As well, research to date has not identified an effective way to improve sexual and psychosocial adjustment for both men with Pca and their partners.

One of the latest interventions to improve sexual and psychosocial adjustment for both men with Pca and their partners is "Proscan for Couples" (67), a randomised control trial of a couples-based intervention that targets the specific challenges couples experience at diagnosis of localised Pca and after RP. Intervention components include psycho-education; cognitive behavioural strategies; couple relationship education focused on relationship enhancement and helping the couple to conjointly manage the stresses of cancer diagnosis and treatment; and specific psychosexual education and sexual communication. The protocol consisted of sexuality intervention DVD plus eight sessions of telephone support by peer support volunteers or professional nurse, planned from post-surgery to six months later.

This study has identified when distress in couple is highest during diagnosis period, and consequently realizing more specific and individual interventions trough a cost-effective and easily translatable approach.

The impact of Pca and hypogonadism on the psychological well-being

It is well-known how Pca bears on psychological well-being. In fact, both the diagnosis and the relative treatment may lead to dramatic consequences, damaging the sexual and, in some cases, the general self-esteem. However, the negative relation between Pca and psychological well-being may be also reinforced by the hypogonadal condition, which, in some cases, may coexist with the cancer.

Some studies have highlighted the impact of testosterone decrease on mood. In particular, a review (68) has evidenced the role of low testosterone levels in the development of anxiety and depression. In fact, it is known that hypogonadal men may suffer with more probability of anxiety disorders and major depressive disorder, compared to men with physiological androgens levels. *Vice versa*, several researches suggest that testosterone-replacement therapy in hypogonadal men may improve mood, alleviates anxiety, and mitigates symptoms of depression. This data remains, however, not replicable in all studies.

The suggestion of a worsening by the side of a low testosterone levels is given by another study (69) investigating the prevalence of sexual dysfunctions, anxiety, depression, and a poorer quality of life in young patients with congenital hypogonadotropic hypogonadism (CHH). As supposed by researchers, low endogenous levels of testosterone might be related to the increased incidence of psychological symptoms.

Hence, since the man with both a diagnosis of a Pca and of a hypogonadism may be of a major risk to develop anxiety disorders or major depressive disorder, this patient should be supported by a psychoterapic intervention, in order to re-establish the global well-being.

Conclusions

Clinical and biological data suggest no clear relationship between testosterone levels and growth of Pca above the range of castration. While no randomized controlled trials have been specifically conducted to answer to this clinical issue retrospective clinical data indicate that TRT may be used safely in highly selected men with Pca. The negative attitudes with respect to testosterone supplementation in men with hypogonadism and Pca may be justified by the relatively low number of clinical and preclinical studies that specifically dealt with how androgens affect Pca biology. More controversial still is the use of TRT in men in active surveillance or at intermediate or high risk of recurrence and treated by curative radiotherapy. In these clinical scenarios, clinicians should be aware that safety data regarding TRT are scanty limiting our ability to

draw definitive conclusions on this important topic. Long-term data and more prospective or randomized studies are needed to conclusively change the current paradigm regarding TRT and Pca growth.

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Footnote

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