Testosterone Replacement Therapy in Prostate Cancer Patients: Is It Safe?

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ABSTRACT

The increasing population of elderly men means there is also an increase in those suffering from late-onset hypogonadism and testosterone deficiency, with all its attending consequences such as reduced libido, erectile dysfunction, metabolic disturbances, cardiovascular disease, decreased bone density and reduced quality of life. The use of testosterone replacement therapy may benefit such patients but remains controversial, especially with regard to the risk it may have on prostate cancer. However, there is no conclusive evidence that testosterone therapy increases the risk of developing prostate cancer nor is there any evidence to suggest that it can convert subclinical or indolent prostate cancer into a clinically significant one. In fact, a number of recent reports have shown that it is safe to give testosterone therapy in patients who have been successfully treated for early prostate cancer. Therefore, the purpose of this review is to discuss the role of testosterone replacement therapy, focusing on those with prostate cancer, as well as the risks and benefits that every physician must consider before commencing treatment.

Key words: *hormone refractory prostate cancer, hypogonadism, quality of life, erectile dysfunction.*

INTRODUCTION

Since the publication of Huggins and Hodges around 65 years ago until now, one of the principles of treating advanced prostate cancer that remains currently used has been reduce testosterone levels as much as possible, which is termed hormonal therapy.[1,2] This is due to the fact that lowering testosterone to a castrate level results in regression of prostate cancer.

Recently, testosterone deficiency has been the subject of many studies, one of which is by Mulligan et al., who reported that 39% of males between 45-85 years of age had a testosterone level of <300ng/dL.[3] Similarly, testosterone deficiency was found in approximately 18%-20% of patients with prostate cancer at the time of diagnosis by Khera et al.[4] In addition, an interesting study by Morgentaler and Rhoden[5] found that amongst 345 men with a testosterone level <250ng/dL and prostate specific antigen (PSA) ≤ 4.0ng/dL, 21% had prostate cancer. This figure was higher than the incidence of prostate cancer in men with normal testosterone levels, which was only 12%. They concluded that an increased risk of prostate cancer was associated with more severe reductions in testosterone. As such, there are two groups of prostate cancer patients suffering from testosterone deficiency with all its undesirable consequences. The first is those who had already had testosterone deficiency when they were diagnosed and the second group is those who are receiving hormonal therapy for prostate cancer and as a result had low testosterone levels.

Our aim is, therefore, to review the safety and efficacy of testosterone replacement therapy for sufferers of prostate cancer and its implications on the course of the disease for those with early and advanced stage cancer.

LATE-ONSET HYPOGONADISM

Late-onset hypogonadism (LOH) is defined as a condition whereby low testosterone levels are associated with clinical signs and symptoms. It usually occurs when testosterone levels are <250ng/dL although some studies have used a threshold of <300ng/dL. Thus, the general consensus is that those with a total testosterone level >350ng/dL do not need testosterone replacement.[6] The most frequent symptoms are erectile dysfunction and low libido; others include metabolic disturbances, lethargy, depression and reduced muscle mass.[6,7] Metabolic disturbances can vary from hyperglycaemia, hyperlipidaemia and reduced bone mineral density, all of which can occur singly or in combination and can be detected by laboratory based investigations and other supporting tests.[6,8]

Clinical signs are usually manifested during the physical examination, including circumferential waist measurement and body mass index,[8] whereas sexual dysfunction may be elicited through the use of the IIEF-5 (International Index of Erectile Function-5) questionnaire.[8] All these features could result in a significant reduction in the quality of life (QoL) as well as possible organ dysfunction that may necessitate further treatment.

INDICATIONS FOR TESTOSTERONE REPLACEMENT THERAPY

The indications for treatment are, amongst others, erectile dysfunction, lowering of libido, decreased muscular function, osteopenia or osteoporosis and metabolic disturbances. With osteopenia and osteoporosis, a longer period of evaluation between 1 to 2 years is required to assess the outcome of testosterone replacement, whilst for other indications the outcome may be evaluated after 3 to 6 months of treatment.[6,7]

Generally, the aim of treatment in these patients is to raise their testosterone levels together with treating other associated disorders. A wide variety of testosterone replacement therapy is already available, ranging from oral tablets and gel patches to injections.[6,8] Each option has its own advantages and disadvantages with regard to efficacy at raising testosterone levels, user friendliness, side effects and cost. For instance, those taking tablets will take relatively longer compared to patients using gel patches, while those receiving injections will experience the fastest rise in testosterone levels.[6,8] The success rate of replacement therapy at raising testosterone levels ranges between 50% to 100% depending on the route of administration and patient compliance. For example, 30-50% of patients on a transdermal preparation may have skin reactions causing treatment failure, compared to injections that will have a 100% success rate.[9] Nevertheless, in those who are compliant, even transdermal gels can be predicted to result in almost 100% of patients achieving average testosterone levels of >300ng/dL, with mean testosterone levels of 415.14ng/dL (range 43 to 918 ng/dL) 7 days after treatment.[10] Another beneficial effect is a reduction in the risk of developing cardiovascular disease manifested by a lowering of cholesterol levels, reduced risk of metabolic syndrome and improved glucose metabolism.[6]

SIDE EFFECTS OF TESTOSTERONE REPLACEMENT THERAPY

Remembering that testosterone stimulates the formation of erythrocytes, one of the side effects of testosterone therapy frequently seen is polycythaemia, especially in those receiving testosterone injections.[10] Other side effects are gynaecomastia, prostate enlargement and lowering of HDL cholesterol; these being more commonly found in obese patients.[6] As previously discussed, the most feared side effect is the potential rise in incidence of prostate cancer in those on testosterone therapy. Nevertheless, reports of studies in the last decade have failed to provide conclusive supporting data on this issue.[6,7,10]

In addition, oral forms of 17-methyl testosterone should no longer be used due to potential liver toxicity.[11] Other less frequent adverse events include psychotic symptoms, excessive libido, aggression and withdrawal symptoms.[12]

Contraindications to testosterone treatment are patients with untreated early prostate cancer and advanced prostate cancer that is still responding to hormone therapy. In rare cases of male breast cancer, testosterone should also not be given.[6] More relative contraindications such as untreated severe congestive heart failure and untreated obstructive sleep apnea must also be considered.[6]

TESTOSTERONE REPLACEMENT THERAPY IN EARLY STAGE PROSTATE CANCER

Since early of this decade, several case series have reported that in those who have been given radical treatment for prostate cancer, be it operative or using radiotherapy, testosterone levels may be safely increased to a point above the lower limit for normal.[13-16] These studies also showed that none suffered from

recurrent cancer during the period of testosterone replacement, which ranged from 19 months to 12 years, as seen in **Table 1**. In addition, an improvement in the QoL was reported by Morales et al.[16] with an improvement in libido and lethargy seen in 4 patients and better erectile function in 2 patients.

More recently Isbarn et al.[17] reviewed the use of testosterone replacement therapy in those suffering from prostate cancer and in whom successful curative treatment had been carried out in the form of radical prostatectomy or radiotherapy (either external beam radiotherapy or brachytherapy). They reported on a total of 116 men ranging in age from 50 to 83 years old with a median follow up of around 12 to 60 months. Indications for testosterone therapy include reduced libido, erectile dysfunction, hyperglycaemia, low energy levels, hot flashes, cognitive impairment and abnormalities in bone densitometry. Testosterone levels were raised to a mean level of 486.9ng/dL post therapy. Amongst these 116 men, only one patient (who had radical prostatectomy) experienced a biochemical recurrence in the form of a PSA rise during follow up[10] (**Table 1**). The authors thus concluded that testosterone therapy is feasible after curative prostate cancer treatment to raise testosterone levels just as it can be used to treat those without prostate cancer, thereby providing patients with all the benefits associated with it such as improved bone and muscle metabolism and a potential reduction of cardiovascular risk factors including dyslipidaemia and diabetes.[8]

Table 1. Reports of effects of testosterone replacement therapy in prostate cancer patients following radical curative treatment[17]

Author	Sample size	Primary Therapy	Follow-up
Kauffman and Groydon[13]	7	Radical prostatectomy	1 – 12 years
Agarwal and Oefelein[14]	10	Radical prostatectomy	9 – 29 months (mean: 19 months)
Sarosdy[15]	31	Brachytherapy	1.5 – 9 years (median: 5 years)
Morales et al[16]	5	Radiotherapy	6 – 27 months (mean: 14.5 months)

TESTOSTERONE REPLACEMENT THERAPY IN ADVANCED STAGE PROSTATE CANCER

As previously mentioned, lowering testosterone levels in prostate cancer patients, particularly in those with advanced stages, is a fundamental concept in its treatment. In fact, giving testosterone to such patients could be considered as providing "fuel for fire" or "food for a hungry tumour".[5]

Nevertheless, in patients with early stage prostate cancer that has been cured successfully, marked by a PSA nadir of less than 0.1-0.2ng/ml, testosterone therapy does not appear to have any significant adverse impact.

In accordance with guidelines that are in general use in Urology clinics[18] the gold standard treatment for advanced stages of prostate cancer remains hormonal therapy in the form of bilateral orchidectomy or injections with a *Gonadotropin Releasing Hormone* (GnRH) agonist together with an anti-androgen. Such patients are bound to suffer from hypogonadism. Moreover, in *hormone refractory prostate cancer* (HRPC) whereby PSA levels continue to rise despite hormonal therapy, this therapy is still maintained whilst combining it with chemotherapy and other supportive treatment.[18]

Of note, there are 2 recent phase 1 studies that have been published regarding testosterone replacement therapy in those with HRPC.

The first involved 15 men with HRPC[19] treated with transdermal testosterone patches at a dose of either 2.5 mg/day, 5.0 mg/day or 7.5 mg/day until they progressed (time to progression: 2-96 weeks). Testosterone increased from castrate to median concentrations of 305 ng/dL, 308 ng/dL and 297 ng/dL for dosages of 2.5 mg/day, 5.0 mg/day and 7.5 mg/day respectively. However, the only improvement in QoL measurement was a slightly significant rise in hand-grip strength after testosterone treatment. Other QoL parameters did not show any significant improvement. The treatment was well tolerated, with no significant adverse events although 1 patient was taken off at 53 weeks due to cardiac toxicity and 1 patient had symptomatic progression in the form of reduced performance status.[19]

The second study looked at 12 patients with castrate-resistant metastatic prostate cancer[20] who were given high dose exogenous testosterone in the form of 5mg transdermal patches that was later changed to 1% testosterone gel. Levels of testosterone rose to an average of 589 ng/dL (range: 342.5-876.0 ng/dL). Although 9 patients progressed, of interest were 7 patients showed a decline in PSA of between 7.9%-49.66% during testosterone therapy. In this study, GnRH agonists were continued if patients had been previously on them already.

One of the ways to reduce the risk of progression is to block the androgen receptors (AR) of prostate

Table 2. Phase I studies of testosterone replacement therapy in hormone refractory prostate cancer[19,20]

Author	n	Skeletal metastases	Dose / Route	Length of therapy (weeks)	Testosterone rise (ng/dL)	PSA before therapy (ng/mL)	Rise in PSA after therapy (ng/mL)	Decrease in PSA after therapy (ng/mL)	New lesions (Bone scan)
Szmulewitz R et al[19]	15	6 (40%)	2.5-7.5mg patch	2-96	Median 271-308 (range: 94-824)	Median 17.7 (5.3-63.6)	12 patients (n/a)	3 patients (16%/20%/43%)	3 patients
Morris MJ et al[20]	12	11 (91.6%)	5mg patch or gel 1%	1-35	Mean: 589 (range: 342.5-876.0)	Median 91 (6-2637)	5 patients (38.4% mean rise, range: 5.6-87.3%)	7 patients (23% mean decrease, range: 7.9-49.7%)	6 patients

cancer cells. Consequently, Tran et al.[21] discovered 2 derivatives of non-steroidal antiandrogens that have a high affinity for androgen receptors. These derivatives, RD 162 and MDV 3100, in fact caused a 100% regression on experimental mice and in a clinical phase I/II study resulted in a PSA decrease in about 43% of patients.

CONCLUSION

Testosterone replacement therapy represents one aspect in the management of patients with prostate cancer, with a good safety profile in terms of side effects when given to those who have had successful curative treatment and can elevate testosterone levels to within the normal range. In addition, testosterone therapy at high dose is well tolerated in those with HRPC even though 75% of patients showed progression. However, with the development of new antiandrogens, this rate of progression may hopefully be reduced in the future.

With regard to the impact of testosterone therapy on quality of life, most studies in this review unfortunately did not evaluate QoL as an outcome measure. Those that did were limited by lack of randomization and small sample size.[14,19] In addition, QoL parameters that did showing an improvement in these studies were limited to decreased hot flashes, increased energy levels and better hand-grip strength only. Future studies should, therefore, focus more on these QoL issues, which after all is one of the primary reasons for giving testosterone therapy in the first place.

Bearing in mind this fundamental change in treatment concept and the number of specialties other than Urologists who are already involved in giving testosterone replacement therapy, it is hoped that the benefits and risks for each individual patient will be weighed carefully by each specialist and that a full pretreatment evaluation be carried out. This should include at the very least a PSA test and digital rectal examination to assess the prostate. Any abnormal findings should prompt referral to a Urologist who might consider further tests such as TRUS (trans-rectal ultrasound) prostate biopsies, as recommended by an international multi-specialty Guidelines panel.[6] Furthermore, regardless of who subsequently manages these patients, a close clinical and biochemical follow up is essential to provide the best individualized care for the patient.

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