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The Role of Testosterone Replacement Therapy Following Radical Prostatectomy

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Hypogonadism is associated with a decreased serum testosterone level and numerous signs and symptoms, such as decreased libido, erectile dysfunction, decreased muscle mass, increased fat deposition, decreased ability to concentrate, and decreased bone mineral density [1–3]. Hypogonadism affects nearly 13 million Americans, with the incidence increasing with age [4,5]. Mulligan and colleagues [4] found that roughly 39% of men between the ages of 45 and 85 years had low testosterone levels. Despite its prevalence, many men who have this condition do not seek treatment.

Unlike women, who have a sudden loss of estrogen during menopause, men experience a gradual 1% to 2% decline in testosterone every year starting at age 30. There are several reasons for decreasing testosterone levels with age. As men age, they have a decline in Leydig cell numbers (primary failure), a decrease in gonadotropin-releasing hormone pulse amplitude (secondary failure), and an increase in sex hormone-binding globulin, all of which result in the reduction of available free or total testosterone [6,7].

Testosterone replacement therapy (TRT) is effective in treating the signs and symptoms of hypogonadism. These benefits include improvements in sexual function, muscle mass and strength, fat distribution, bone density, cognition, and mood [2,3,8,9]. Although hypogonadism also was shown to have an increased association with obesity and diabetes [10], TRT improves insulin resistance and weight loss. Pitteloud and colleagues [11] demonstrated that insulin resistance significantly improved after human chorionic gonadotropin stimulation. Wang and colleagues [12] found

a significant increase in lean body mass and decrease in fat composition in hypogonadal men who were treated with transdermal testosterone replacement.

Hypogonadism occurs frequently among men who have prostate cancer. Yamamoto and colleagues [13] found that among men scheduled for a radical prostatectomy, approximately 18% had low testosterone levels. Mulligan and colleagues [4] found that 20% of men who had prostate disease or disorders were hypogonadal. Because prostate cancer and hypogonadism are much more common in men as they age, patients who have prostate cancer are a subset of men who are more likely to be hypogonadal.

The association between testosterone replacement therapy and the development of prostate cancer

In 1941, Huggins and Hodges [14] first demonstrated that a reduction in testosterone by castration caused metastatic prostate cancer to regress and that administration of exogenous testosterone promoted prostate cancer growth; however, current data have demonstrated that low testosterone levels are more likely to be associated with prostate cancer [15]. Morgantaler and Rhoden [15] found that cancer was detected in 21% of men with a low testosterone level of 250 ng/dL or less compared with 12% of men with a testosterone level greater than 250 ng/dL. Hoffman and colleagues [16] demonstrated that men with low testosterone values (<300 ng/dL) had a 47% chance of having prostate cancer on transrectal ultrasound biopsy compared with only 28% of men with normal testosterone levels ($P = .018$). Recently, Yamamoto and colleagues [13] showed that preoperative testosterone serum levels were

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an independent and significant predictor of PSA failure after radical prostatectomy in patients who had clinically localized prostate cancer. In this study, 5-year prostate-specific antigen (PSA) failure-free survival rates of the patients with preoperative low testosterone levels were significantly lower than those with normal testosterone values (67.8% versus 84.9%, respectively; $P = .035$). These findings suggest that low circulating testosterone levels may not have a protective effect against the development of prostate cancer. In fact, several studies showed that low testosterone levels were associated with more aggressive and higher-grade prostate cancer [16,17].

There is further evidence to support the belief that increased testosterone levels do not increase the risk for prostate cancer and growth. PSA values have not been shown to increase significantly after TRT [18–20]. In addition, prostate cancer exerts an inhibitory effect on testosterone synthesis, with studies demonstrating a significant increase in testosterone after a radical prostatectomy [21]. Finally, TRT in hypogonadal and eugonadal men has not been shown to increase prostate volume significantly [20,22].

Studies also report that TRT is a safe treatment for patients who are at high-risk for prostate cancer development. Rhoden and Morgentaler [23] treated 55 men with benign prostate biopsies and 20 men who had high-grade prostatic intraepithelial neoplasia (HGPIN) with TRT. The investigators followed these men for 1 year and found that there was no significant change in PSA in either group. Testosterone values improved significantly in both groups. A single patient who had HGPIN was diagnosed with prostate cancer based upon a biopsy after an abnormal digital rectal examination. Rhoden and Morgentaler concluded that men who have prostatic intraepithelial neoplasia (PIN) do not have a significantly greater risk for developing prostate cancer than do men without PIN after 1 year of TRT. If TRT is safe in treating men who have HGPIN, then administration of TRT to selected men following a radical prostatectomy (with negative margins and no biochemical recurrence) may be safe as well.

Marks and colleagues [24] studied the effect of TRT on prostate tissue in men who had late-onset hypogonadism. In this randomized, double-blinded, control trial, 40 hypogonadal men were treated with 150 mg of testosterone enanthate or placebo intramuscularly every 2 weeks. Prostate biopsies were performed at baseline and at the end of 6 months. Serum testosterone increased

from 282 ng/dL to 640 ng/dL in the treated men. In contrast, there was no significant change in testosterone levels within the placebo-treated group (282 to 273 ng/dL). Testosterone and dihydrotestosterone (DHT) concentrations within the prostate did not change significantly in either group. Treatment-related changes in prostate histology, PSA, tissue biomarkers, gene expression, or cancer incidence or severity were not evident. In a related study, Heracek and colleagues [25] found no significant correlation between intraprostatic and serum testosterone levels in patients who had benign prostatic hyperplasia or prostate cancer. In this study, serum samples were analyzed for testosterone and DHT in 75 patients who had prostate cancer and 51 patients who had BPH. Significantly higher intraprostatic dihydroepiandrosterone concentrations were found in patients who had prostate cancer than in men who had BPH (8.9 ng/dL versus 6.4 ng/dL, respectively; $P < .01$). Similarly, there were higher intraprostatic concentrations of testosterone in men who had prostate cancer as compared with men who had BPH (4.6 ng/dL versus 3.4 ng/dL, respectively; $P < .05$); however, no differences were found in serum levels between the two groups of patients. Furthermore, there was no correlation between tissue and serum testosterone and DHT levels in either group of patients. These data support the safety of TRT in hypogonadal patients and demonstrate that there is no association between serum and intraprostatic levels of testosterone. There seems to be a threshold at which the prostate becomes saturated with testosterone and higher levels of serum testosterone do not affect intraprostatic levels.

TRT is withheld from many patients after surgery for prostate cancer for fear of exacerbating latent cancer cells; however, in each of the three small published series of TRT after a radical prostatectomy, there was not a single documented PSA increase [26–28]. In all three series, testosterone values increased significantly after initiation of TRT with an average follow-up of 21 months. Similarly, Sarosdy [29] evaluated TRT in patients with prostate cancer who were treated with brachytherapy. In this study, 31 men were followed for a median of 5 years after starting TRT. Although testosterone levels increased significantly, no patient stopped TRT because of cancer recurrence, and no patient experienced cancer progression. Although there are limited data in the literature evaluating the long-term safety of TRT in men who are treated for prostate cancer, early results suggest that TRT is safe within this population.

The importance of testosterone replacement therapy in erectile preservation following radical prostatectomy

Androgens play an important role in penile rehabilitation and overall erectile function. Non-responders to phosphodiesterase type 5 inhibitors (PDE5i) often are hypogonadal men. TRT in these men converts PDE5i nonresponders to PDE5i responders [30–32]. Guay and colleagues [33] demonstrated that hypogonadal men not treated with androgens had a lower response rate to sildenafil citrate than did men receiving TRT (75% versus 85%, respectively). Similar findings were observed by Shabsigh and colleagues [31]. They conducted a randomized, placebo-controlled trial in 75 men who had hypogonadism (testosterone <400 ng/dL) who failed to respond to sildenafil citrate. Half of these patients received 5 g/d of transdermal testosterone gel. Testosterone-treated subjects had greater improvements in erectile function at 4 weeks than did those who received placebos. The results of these two studies can be explained by the fact that increased testosterone levels have been associated with greater phosphodiesterase type 5 and nitric oxide synthase activity within cavernosal tissue [34–37]. Enhancement in erectile dysfunction treatment response may reflect the actions of testosterone on the up-regulation of NOS isoenzymes in the corpora cavernosa [35]. Thus, testosterone plays an important role in erectile function and in augmenting the effects of PDE5i.

Testosterone also has an important role in cavernosal nerve function and growth. Schirar and colleagues [38] demonstrated that androgen receptors were present in approximately 40% of neurons of the major pelvic ganglion innervating the corpora cavernosa of the rat penis. They also showed that in the major pelvic ganglion, 87% of the neurons contained nitric oxide synthase. These results suggest that androgens, which are known to modulate penile erections, may do so by regulating nitric oxide synthase within the major pelvic ganglia by way of direct interaction with ganglionic neurons. In another study, Baba and colleagues [39] demonstrated that there was a significant reduction in nerve fibers in the corpora cavernosa and both dorsal nerves in castrate rats. Rogers and colleagues [40] found that in castrated rats, the diameter of the myelinated and nonmyelinated axons of the dorsal penile nerve were significantly smaller than were those of the sham-operated rats. When these animals were given testosterone, the nerve fibers and myelin sheath size appeared

similar to those in the sham-operated group. Finally, Syme and colleagues [41] studied 45 rats that underwent bilateral cavernosal nerve neurotomy, followed by unilateral nerve graft using the genitofemoral nerve. Then rats were randomized to castrate, intact, and testosterone-treated arms. At 3 months, grafts were explored, and electrostimulation was performed with intracavernous pressure responses recorded. Then grafted nerves were harvested for immunohistochemical analysis. Castration resulted in a decreased erectile response to electrostimulation following nerve grafting, and castrate animals had lower neuronal nitric oxide synthase axon counts than did intact animals. It is clear from these several studies that androgens play an important role in cavernosal nerve function and growth.

There is substantial evidence to support that DHT, not testosterone, is the more active and potent androgen in preventing erectile impairment [42–44]. Lugg and colleagues [42] found that DHT was the active androgen in the prevention of erectile failure seen in castrated rats and that this effect may be mediated, at least partially, by changes in nitric oxide synthase levels within the penis. DHT may be more effective in improving erectile function because of its higher affinity for binding with the androgen receptor [45]. The prostate is a major source of DHT in men; thus, it is not surprising that there is a significant reduction in DHT following radical prostatectomy. Because DHT has been shown to be the major source for maintenance of erectile function, it seems likely that patients who have undergone radical prostatectomy may be more susceptible to experiencing erectile dysfunction than are men who still have their prostates.

Summary

Hypogonadism is highly prevalent in older men and men who have prostate cancer. The symptoms of hypogonadism, such as depression, decreased libido, erectile dysfunction, and decreased bone mineral density, can impair a man's quality of life significantly. Moreover, we know that testosterone plays an important role in erectile preservation by improving the effects of PDE5i and in the growth and function of cavernosal and penile nerves. There are now compelling data to suggest that TRT in normal and high-risk men does not increase the risk for prostate cancer. In the few studies of men treated with TRT after a radical prostatectomy, there have been no biochemical recurrences. Based

on these data, it is difficult to justify withholding TRT in men following a radical prostatectomy. If we do not lower the testosterone levels of eugonadal men after a radical prostatectomy, how can we justify not replacing testosterone levels in hypogonadal men to make them eugonadal following a radical prostatectomy?

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