

The Prostate as an Endocrine Organ Its Modulation of Serum Testosterone



Kevin R. Loughlin, MD, MBA

KEYWORDS

- Prostate cancer • Benign prostatic hypertrophy • Testosterone • Dihydrotestosterone • LH • FSH
- Inhibin

KEY POINTS

- Provocative findings suggest that the prostate gland may have more endocrine functions than previously appreciated.
- Prostate cancer, but not benign prostatic hyperplasia, appears to exert some modulation of the hypothalamic-pituitary axis.
- The increase of serum testosterone following a radical prostatectomy seems to be, at least, in part influenced by a factor or factors produced by prostate cancer.
- Inhibin and dihydrotestosterone have been proposed as possible substances elaborated by prostate cancer that influence the hypothalamic-pituitary axis and thereby modulate postprostatectomy serum testosterone levels.

INTRODUCTION

Aside from nonmelanoma skin cancer, prostate cancer is the most common cancer among men in the United States,¹ and benign prostatic hyperplasia (BPH) is the most common benign tumor found in men.² Until recently, its endocrine functions and possible influence on the hypothalamic-pituitary axis have been relatively understudied. This review summarizes the current understanding of the potential endocrine functions of prostate cancer and benign prostate tissue.

Emerging Observations

In 1998, Miller and colleagues³ reported on 63 men, ages 43 to 67 years, who had a phlebotomy performed immediately before and one year following a radical retropubic prostatectomy. Serum testosterone, percent-free testosterone, dihydrotestosterone (DHT), estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), serum hormone-binding globulin (SHBG), and prolactin were measured. They reported that

following radical prostatectomy there was a statistically significant increase in serum testosterone, free testosterone, estradiol, LH, and FSH ($p < 0.0001$) and a decrease in serum DHT ($p < 0.0001$). There was no statistically significant correlation between any serum hormone and sample storage time, patient age, or prostate volume. In addition, serum hormone changes did not correlate with pathological stage or histological grade for these patients. The investigators postulated that DHT and inhibin were 2 known factors produced by the prostate that could induce this effect.

In 2002, Madersbacher and colleagues⁴ followed the Hopkins study with a diverse group of patients, 49 underwent a radical prostatectomy for prostate cancer, 51 underwent a transurethral resection of the prostate (TURP) for BPH, and 46 were managed conservatively for lower urinary tract symptoms. Serum levels of testosterone, LH, and FSH were measured at baseline and 6 and 12 months later in all patients.

There were no significant endocrine changes observed in the observation or TURP groups at 6

Vascular Biology Research Laboratory, Boston Children's Hospital, Harvard Medical School, Boston, MA 02114, USA

E-mail address: kloughlin@partners.org

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and 12 months after baseline. However, in contrast, in the prostate cancer group followed after radical prostatectomy, the LH increased from 5.2 to 8.9 mIU/mL ($p = 0.0004$) and the FSH increased from 5.7 to 9.3 mIU/mL ($p = 0.0003$) 12 months after radical prostatectomy ($p = 0.0003$). The increase of total testosterone from 3.9 to 4.4 ng/mL did not reach statistical significance ($p = 0.18$). At 12 months after radical prostatectomy, no changes from baseline were observed in patients with a Gleason score of 2 to 6, but in those patients with a Gleason score of 7 to 10, the serum testosterone more than doubled. However, the LH and FSH levels were comparable in both low- and high-grade tumors at 12 months.

The investigators concluded from this study that prostate cancer and not benign prostate tissue mediated the changes in the hypothalamic-pituitary axis and that the changes were more pronounced in the higher grade tumors.

In 2010, Olsson and colleagues⁵ examined the serum levels of testosterone, DHT, SHBG, LH, and FSH in 53 patients before and 90 days after radical prostatectomy. Inhibin B levels were analyzed before and 90 days postoperatively in 44 patients.

LH levels increased from 3.24 ± 0.32 mIU/mL to 4.97 ± 0.48 ($p = 0.0001$), and FSH levels increased from 6.62 ± 0.88 to 8.04 ± 1.1 mIU/mL ($p = 0.0001$), and DHT decreased from 482 ± 39.7 pg/mL to 419 ± 35.7 pg/mL ($p = 0.028$).

However, there were no significant changes in preoperative and postoperative levels in testosterone, free testosterone, or SHBG. Of additional importance was the finding that the inhibin B levels were unchanged from preoperative to postoperative levels (166.3 ± 13.5 vs 167.7 ± 12.1 ng/mL). These investigators also observed that the Gleason score was not correlated with the baseline serum androgen levels or changes in the androgen levels 3 months after the radical prostatectomy.

In 2013 Gacci and colleagues⁶ studied 100 patients with clinically localized prostate cancer who were treated with a radical retropubic prostatectomy. Serum levels of testosterone, LH, and FSH were measured at baseline and 1 and 3 months postoperatively.

At 1 month after radical prostatectomy, serum testosterone levels were decreased from 15.3 to 13.8 nmol/L ($p = 0.021$), however, by 3 months the testosterone level had increased to 14.4 nmol/L ($p = 0.372$). In contrast the log LH level was increased at 1 and 3 months postsurgery compared with the baseline (baseline vs 1 month log LH 0.54 vs 0.68 mIU/mL $p < 0.0001$), and at 3 months it remained elevated with log LH 0.54 versus 0.65 mIU/mL ($p < 0.0001$).

Similarly, the postsurgery FSH levels were elevated. At 1 month, the log FSH level increased from 0.74 to 0.80 mIU/mL ($p = 0.0001$) and remained elevated at 3 months log FSH (0.74 to 0.82 mIU/mL; $p < 0.0001$).

The investigators interpreted their results as suggesting that the testosterone was transiently decreased at 1 month after radical prostatectomy and the elevated LH observed at 1 month persisted. The serum T had returned to almost preoperative T levels with a persistent LH elevation, which was consistent with a compensated hypergonadotropic hypogonadism 3 months after radical prostatectomy.

The Putative Role of Inhibin

It would appear that the prostate elaborates a factor or factors that interact with the hypothalamic-pituitary axis and thereby influences postprostatectomy testosterone levels. Walsh has speculated that this substance might be inhibin.⁷

Inhibin A and B are 2 glycoproteins that are secreted by Sertoli cells in the testes and granulosa cells in the ovaries and inhibit FSH by direct action on the pituitary.⁸ Risbridger and colleagues⁹ demonstrated an elevated expression of inhibin alpha in prostate cancer. In addition to its role in the reproductive tract of men and women, Balanathan and colleagues¹⁰ have demonstrated the inhibin alpha subunit to be pro-tumorigenic and prometastatic and is associated with extracapsular spread in advanced prostate cancer.

However, as mentioned earlier, although Olsson and colleagues⁵ found a 53% increase in serum LH and a 21% increase in serum FSH and a 13% decrease in DHT following radical prostatectomy, they found the serum inhibin B levels were unchanged postoperatively from preoperative levels.

Additional study regarding the possible relationship between inhibin and the low testosterone levels in patients with hypogonadal prostate cancer was provided by Lackner and colleagues.¹¹ They entered 126 men with prostate cancer and 70 men with BPH in their study. The serum inhibin levels did not differ significantly between the patients with BPH and those with prostate cancer (150.0 vs 131.75 pg/mL, $p = 0.062$), between those with hypogonadal and eugonadal disease (143.0 vs 146.5 pg/mL, $p = 0.573$), or those with low-grade and high-grade cancer (151.5 vs 146.0 pg/mL, $p = 0.830$). Men with higher grade cancer had lower levels of serum testosterone than did those with low-grade cancer (3.49 vs 4.09, $p = 0.056$).

Future Directions

There are several intriguing questions regarding prostate cancer and serum testosterone:

1. Do the serum T and the gonadotropins change over time postoperatively and does recurrent prostate cancer interfere with the hypothalamic-pituitary axis? If so, could a delayed but gradual decrease in serum testosterone herald recurrent prostate cancer and function as a surrogate biomarker?
2. Will further studies confirm the initial observations that malignant, but not benign, prostate tissue mediates the observed effect on serum testosterone?
3. If prostate cancer is the mediator of the observed changes in serum testosterone, does a higher grade cancer cause a more profound depression?
4. If subsequent studies confirm that inhibin is not the vehicle for the observed changes in testosterone, then what substance or substances are the mediators?

SUMMARY

For many years there has been an ongoing controversy regarding the influence of serum testosterone levels and the development of prostate cancer. In 2015, the author and his colleagues reported a literature review that confirmed this controversy. They identified 45 studies that examined this relationship and 18 found a relationship between prostate cancer and low testosterone, 17 reported a relationship with high serum testosterone, and 10 found no relationship between the serum testosterone level and prostate cancer.¹²

Walsh and his group made the observation that prostate cancer influenced testosterone level almost a quarter of a century ago. For most of the subsequent years, that observation has gone largely ignored and underinvestigated. There has been a plethora of articles reporting conflicting results examining the hypothesis that serum testosterone influences the development of prostate cancer. It is long overdue to begin looking in the opposite direction that it may be the prostate cancer that influences the serum testosterone and not the other way around.

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