George Yu*, Charles Mylander, Abdulmaged Traish and Thomas Jarrett

Circulating levels of gonadotropins before and after prostate ablation in cancer patients

Abstract

Background: The prostate gland synthesizes a host of hormones, prostaglandins and growth factors. It is not clear if such biochemical factors modulate the hypothalamic/pituitary (H-P) gonadal axis.

Aim: To determine the influence of the prostate gland on the hypothalamic-pituitary axis feedback system and changes in circulating hormone levels before and after cryoablation of the entire prostate.

Methods: In 37 consecutive patients with localized prostate cancer who underwent total cryoablation we investigated the circulating levels of testosterone, estradiol, progesterone, sex hormone binding globulin (SHBG) luteinizing hormone (LH), follicle stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEAS), prolactin, insulin-like growth factor-1(IGF-1) and prostatic specific antigen (PSA) from 3 years prior to diagnosis to 3 years after initiating treatment.

Results: The levels of LH and FSH were significantly elevated in most patients up to 3 years after surgery. No significant changes were observed for the other hormones, with a decrease in PSA as expected.

Conclusion: LH and FSH levels rise after ablation of the prostate gland and the levels remain high for up to 3 years after surgery, which suggests that the prostate gland may influence the H-P feedback axis.

Keywords: follicle stimulating hormone (FSH); gonadotropins; luteinizing hormone (LH); prostate ablation; prostate cancer.

*Corresponding author: George Yu, MD, Clinical Professor of Urology, George Washington University Medical Center and Aegis Medical and Research Associates, 122 Defense Hwy, Suite 224, Annapolis, MD 21401, USA, Phone: +1-410-897-0540, Fax: +1-410-224-4703, E-mail: George.yu8@gmail.com
George Yu: Department of Urology, George Washington University Medical Center, Washington DC, USA
Charles Mylander: Naval Academy, Department of Statistics, Annapolis, MD, USA
Abdulmaged Traish: Department of Urology, Boston University School of Medicine, Institute of Sexual Medicine, Boston, MA, USA
Thomas Jarrett: Department of Urology, George Washington University Medical Center, Washington DC, USA

Introduction

With increased awareness of the disease, refinement prostatic specific antigen (PSA) testing and the use of 'super-saturation' biopsies, more men are receiving curative treatment for localized prostate cancer. Radical prostatectomy, brachytherapy, cryotherapy and HiFu are treatment options available for the early stages of the disease.

It should be noted that limited information is available on the impact of prostatectomy or partial prostate ablation on the overall endocrine milieu and its potential consequences. Miller et al. [1] investigated the influence of radical prostatectomy on the hypothalamic pituitary axis and circulating hormone levels. Following radical prostatectomy in 63 men with clinically localized prostate cancer, there was a statistically significant increase in serum testosterone, free testosterone, estradiol, luteinizing hormone (LH) and follicle stimulating hormone (FSH) (p<0.0001), and a statistically significant decrease in serum dihydrotestosterone (DHT) (p<0.0001). These data suggest that the prostate may secrete a substance or substances that modulate negative feedback control to pituitary gonadotropin secretion.

Similarly, Olsson et al. [2] examined the potential physiological role of the prostate as an active endocrine organ and the hormonal changes after radical prostatectomy (RP) in 55 healthy men with localized prostate cancer. There was a 53% increase in serum LH (p<0.0001), a 21% increase in serum FSH (p<0.0001), and 13% decrease in DHT levels (p<0.03). No significant changes were noted in any other serum hormones investigated. The authors suggested that radical prostatectomy leads to significant increases in serum gonadotropins and significant DHT decrease, and these changes are independent of inhibin B levels. In another study, Bantis et al. [3] examined hormone levels in 70 patients with prostate cancer before and after radical prostatectomy. In the group of 66 patients there was a statistically significant increase in serum T (p<0.001), LH (p=0.004) and FSH (p<0.001), and statistically significant decrease in serum DHT (p<0.001). These findings of increased LH and FSH and decreased DHT after radical prostatectomy suggest that the gland may secrete a substance that induced a negative feedback

to the pituitary gonadotrophin secretion. These observations are supported by findings from other studies [4–9].

Many of the aforementioned studies have determined circulating hormone levels mostly in patients after radical prostatectomy. In order to address whether the changes in hormone levels are linked with prostate ablation, we initiated a longitudinal study of men undergoing cryoablation of the gland for localized prostate cancer. One key and important characteristic of this study is that we documented the biochemical hormonal status of the patients enrolled in this study up to 36 months before the diagnosis of cancer was made and they were followed up for an equivalent period after treatment. This study design provides a unique opportunity to define the changes in the circulating hormones before and after prostatectomy to address this fundamental question of whether the prostate acts as an endocrine gland and exerts a feedback control mechanism on the H-P gonadal axis.

Figure 1 Age at time of cryosurgery.
Mean, 65.8 years, standard deviation, 7.5 years, median, 64.9 years, n=37.

and rectal tissues. The technological advancement of using argon to freeze tissues to –187°C and reheating back up to room temperature with helium all within 7 min cycles permits good control of the ablative procedure without jeopardizing adjacent tissues. All procedures are performed under sonographic guidance, thereby shaping the 'ice ball' to fit the prostate anatomical shape and setting the limits of freezing to the anatomical landmarks of the posterior/anterior and lateral margins of the prostate gland. A typical histological finding (Figure 2) shows the result 1 year after the ablative procedure.

Experimental design and methods

Patient selection

This study was approved by the Institutional Review Board (IRB) and written informed consent forms were obtained from all patients. We studied hormone profiles of 37 consecutive cases of patients who underwent cryosurgery treatment for localized prostate cancer from a clinical pool dating from 1997 to the beginning of 2007.

The hormonal database came from men seen in the outpatient clinic for up to 3 years for reasons other than prostate cancer as part of our longitudinal database on aging men. Patients were scheduled for evaluation at 6-month intervals. Prostate nodules on rectal examination or PSA elevation prompted a prostate biopsy to rule out prostate cancer.

Men with histological diagnosis of localized prostate cancer stage T1c and T2 with Gleason scores of 6 and 7 were invited to participate in the study. The 37 men were between the ages of 50 and 78 years (mean age of 65.8 years) and elected to have cryosurgery (Figure 1). Patients were excluded if there was a history of diabetes, or if they were on medications that could alter their endocrine profile. After diagnosis of localized prostate cancer and treatment, we followed these 37 patients with serum hormone determinations for up to 3 years after surgery. One surgeon performed all the procedures.

Surgical procedure

Cryosurgery involves controlled freezing ablation with sonographic guidance. The surgeon ablates the entire prostate gland, but preserves the rectal wall, the superior and anterior margins, exclusive of seminal vesicles and the lymph nodes. Compared to surgery or radiation, cryosurgery is the least traumatic to adjacent bladder neck
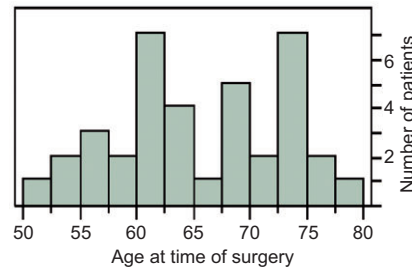
Determination of hormone profiles

We have been compiling a database of patient hormonal profiles at 6-month intervals in the aging male clinic. The patients selected for the study had hormone profiles taken before and after treatments.

All tests were done through standardized procedures by Labcorp commercial laboratory at the hospital and clinic. All serum samples were obtained between 7 and 10 a.m. for total testosterone (ng/mL) by immunochemiluminometric assay (ICMA), bioavailable testosterone (ng/dL) by radioimmunoassay (RIA) and $(NH_4)_2SO_4$ precipitation, free testosterone (pg/mL) by RIA, sex hormone binding globulin (SHBG) (nmols/L) or serum hormonal binding globulin by ICMA, estradiol (pg/mL) by ICMA, progesterone (ng/mL) by ICMA, LH (mIU/mL) by ICMA, FSH (mIU/mL) by ICMA, prolactin (ng/mL) by ICMA, insulin like growth factor-1 (IGF1) (ng/mL) by ICMA, DHEAS (ug/mL) by ICMA, prostatic specific antigen (ng/mL) by electrochemiluminescent immunoassay (ECLIA), and hematocrit (%) by automated cell counter, were obtained from most subjects every 6 months and up to 3 years at the end of study. Inhibin and dihydrotestosterone values were not obtained.

Because of non compliance to regular visits to outpatient clinics, we were able to collect a total of 163 serum samples for analysis, with only 44 serum samples before the diagnosis of prostate cancers and 119 serum samples after surgery. Serum samples dated back up to 3 years before surgery and up to 4 years after surgery at the end of the study.

For comparison with the patients who underwent cryosurgery, we used the endocrine database of patients from our clinic for aging men. We examined the cross-sectional age relationship to LH and FSH and all three forms of testosterone from patients with ages 20 to 90 who did not undergo any prostate surgery. The samples were from their initial baseline hormone profiles performed in a clinic visit before any treatments. We then compared the above data to the hormonal changes in the selected subjects before and after surgery as the two periods of study.
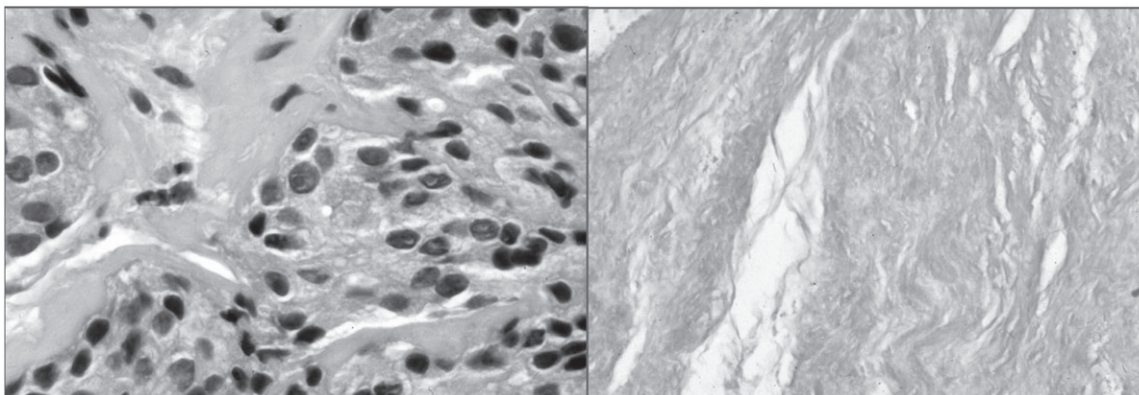
Figure 2 Prostate tissue before and after cryosurgery.
Left panel, Gleason 7 adenocarcinam before surgery. Right panel, fibrotic tissue after surgery.

Statistical analyses

The data were compiled using Excel and the statistical analysis was done using JMP (a statistical package by SAS Institute Cary, NC, USA). Linear regression analysis was used to define patterns and trends and then paired t-tests were done comparing hormone levels before and after surgery. The paired t-test was used to determine if the linear regressions identified as likely to be impacted by surgery could be confirmed on individuals. Linear regression analyses were also done on the hormone levels on a population of patients that were not suspected of having prostate cancer to establish trends as a function of age.

Results

LH and, FSH levels remained constant before diagnosis and surgery but showed significant rates of increases in a period of over 3 years after surgery. But in the cross-sectional age relationship of LH (group who did not have any surgery), there was essentially no increase in LH as a function of age with a positive rate of change of 0.040 units per year (p=0.209) shown in Figure 3. In the study group of 37 men, when we divided the periods before and after surgery, the pre-operative LH showed a positive rate of change of 0.611 units per year with no significance (p=0.445), but the post-operative LH showed a significantly positive rate of change of 2.067 units per year (p=0.0003) shown in Figure 4.

The cross-sectional age-related increase for LH was only 0.040, in contrast to the 37 men who underwent surgery and who showed a steeper LH slope of 2.06 (p=0.0003) over 3 years after surgery. In the paired t-test we had 18 patients with LH values taken up to 147 days before surgery that could be compared with values taken in the 1-year interval centered on the time 1 year after surgery. The average increase was 1.68 mIU/mL and the

null hypothesis that the increase was zero was rejected in favor of the hypothesis that there was an increase with p=0.0306. In paired t-tests pairing patients with LH values taken 1 and 2 years after surgery, there was no significant difference and the same was true with pairs where LH values were determined 2 years and 3 years after surgery. Thus, it appears that there is a significant increase in LH levels a year after surgery and the increased level is maintained (Table 1).

In the cross-sectional age relationship of FSH (the group who did not have any surgery), there was a similar positive change of 0.161 mIU/mL per year (p=0.006), shown in Figure 5. Likewise, in the group of 37 patients, the pre-operative FSH showed a non-significant positive slope of 0.414 (p=0.651), but the post-operative FSH had a significantly positive rate of change of 2.863 mIU/mL per year (p=0.0002), shown in Figure 6.

The cross-sectional age-related increase in FSH showed an increase of 0.161 mIU/mL, in contrast to those who underwent surgery, showing a steeper positive FSH slope of 2.863 mIU/mL (p=0.0002) up to 3 years after surgery. In exploring the change in FSH values in patients before and after surgery, the same pattern was found as in LH. There was a significant increase in the mean value after surgery compared with before surgery. The mean increase in the first year was 2.87 mIU/mL which gave a one-sided p=0.0440. There was not a significant change between years 1 and 2 or between years 2 and 3. The first year after surgery showed the most dramatic increase with the following 2 years showing persistent but minimal further changes.

By linear regression analysis, the total testosterone, bio-available testosterone, and free testosterone showed an increase after surgery, but paired t-tests did not show significance.

The linear regressions for all other hormonal measurements, including estradiol, progesterone, prolactin,
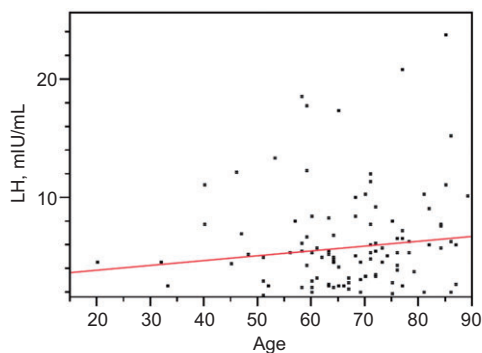
Figure 3 Cross-sectional LH Level (mIU/mL) as a function of age. LH levels in patients in their first visit to the urologist; slope, 0.041 units per year, p=0.206.

DHEAS, SHBG and IGF1, did not show significant changes before or after surgery. For individual patients, however, comparing their IGF1 levels before and after surgery showed an interesting pattern. Here there was an increase in IGF1 levels between the period before surgery and the year after, which had a two sided p=0.0592. After a year,

the increase seemed to fade away with time, but our sample sizes were small and the results not statistically significant. The PSA showed a negative slope as expected after surgery. The mean PSA decreased from 6.5 ng/mL in the year before surgery to 1.1 ng/mL by the years after surgery.

Discussion

The key finding of this study is the documentation of the longitudinal durability of LH and FSH increase (greater than expected changes by age alone) of these patients up to 3 years after surgery. After reviewing the published literature and to the best of our knowledge, we believe that this study is the first to demonstrate the changes in circulating hormone levels 3 years before surgery to 3 years after surgery with the documentation of changes after prostate cryoablation. These circulating hormones may be attributed to the role of the prostate in a feedback mechanism that is yet to be elucidated. Indeed, other investigators
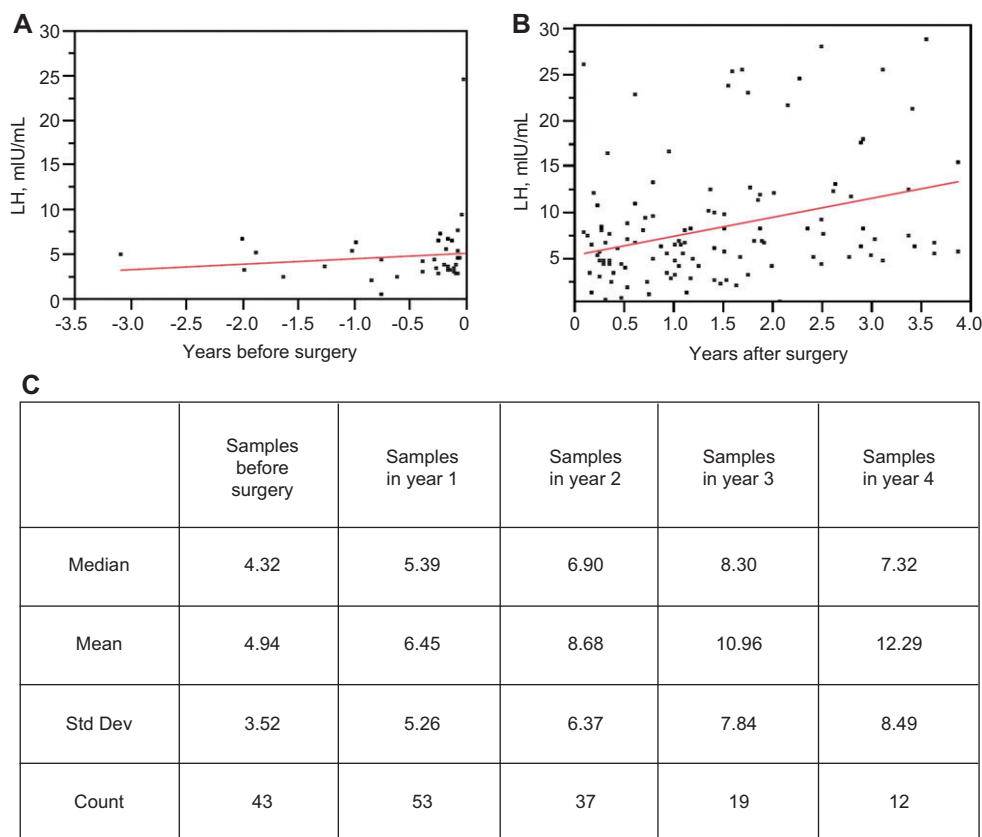

	Samples before surgery	Samples in year 1	Samples in year 2	Samples in year 3	Samples in year 4
Median	4.32	5.39	6.90	8.30	7.32
Mean	4.94	6.45	8.68	10.96	12.29
Std Dev	3.52	5.26	6.37	7.84	8.49
Count	43	53	37	19	12

Figure 4 LH (mIU/mL) before and after cryosurgery.
Panel A, linear fit using observations before cryosurgery; slope, 0.611 units per year, p=0.445. Panel B, linear fit using observations after cryosurgery; slope, 2.067 units per year, p=0.0003. Panel C, median and mean LH samples before surgery and each year after surgery, 1, 2, 3, 4th year.

Hormone	1st Period	2nd Period	Increase, mIU/mL	One-side p-value for increase	Two-side p-value for not zero	Sample size, mIU/mL
LH	Before S	Year 1	1.68	0.031	0.061	18
	Year 1	Year 2	−0.7	0.719	0.562	10
	Year 2	Year 3	0.06	0.482	0.963	12
FSH	Before S	Year 1	2.87	0.044	0.088	19
	Year 1	Year 2	−0.82	0.898	0.204	10
	Year 2	Year 3	1.41	0.896	0.209	11

Table 1 Average increases in LH and FSH levels 3 years after cryosurgery.

This presents evidence that both LH and FSH levels increase in the first year after cryosurgery and then remain level for the next 2 years. Before S, the interval from 2 to 147 days before surgery. Year 1, the interval from 180 to 511 days after surgery. Year 2, the interval from 558 to 858 days after surgery. Year 3, the interval from 908 to 1221 days after surgery. If more than one sample was taken in the interval before surgery we used the one farthest in time from the date of surgery. In the year intervals, if there was more than one sample, the one nearest to the middle of the interval was used. The p-values are for a matched t-test. As an increase was found by the linear regression analysis it was conjectured there would be an increase after cryosurgery, thus a one-sided p-value is used to test for significance for an increase in the first year.

have reported similar findings but for shorter durations of 1 year after surgery.

The classical feedback mechanism, which regulates LH and FSH levels, is attributed mainly to circulating levels of secreted testosterone and its metabolites estradiol and DHT. However, the findings of this study and others clearly suggest that other mechanisms are coming into play and that end organs, such as the prostate, may contribute to an important role via secretion of biochemical substances that feedback on the H-P Axis and regulate the levels of LH and FSH.

Several potential mechanisms may be invoked in this regulation; these include the endogenous levels of DHT, which decrease subsequent to prostate ablation. If DHT is among the players that feedback on the H-P Axis, one may postulate that reduced synthesis and release of DHT after prostatectomy could induce increased LH and FSH secretion and release due to the loss of feedback mechanism, normally regulated by the endogenous levels of DHT.

Olsson et al. [2] studied 55 healthy men with localized prostate cancer who underwent surgery and had both pre- and post-operative serum and urine hormonal profiles done for analysis. The endpoint was 90 days after surgery. LH had risen by 53%, FSH increased by 21%, DHT had decreased by 13%. The hormone changes were independent of inhibin B. Urinary metabolites of DHT were also measured and found to decrease after prostatectomy, again suggesting that the prostate gland showed intracrine activity. The prostate may be a significant source of endogenously synthesized DHT. The reduced DHT levels in plasma and urine after surgery may be the stimulus to increase LH and FSH as part of the feedback mechanism.

However, Schaison et al. [10] found that even a 3-month period of administration of DHT did not seem
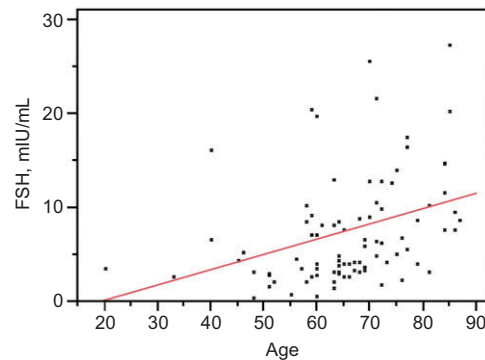

Figure 5 Cross-sectional FSH Level (mIU/mL) as a function of age. FSH levels in patients in their first visit to the urologist; slope, 0.163 units per year, p=0.008.

to effect or lower LH in both normal and hypogonadal men and therefore no systemic affect had occurred. Unfortunately, this may not provide adequate explanation because exogenously administered DHT may not be sufficient to mimic the physiological circulating levels of DHT and the fact that SHBG binds DHT very strongly, may confound the observations of the study by Schaison et al. [10]. In recent studies, in which DHT was administered in sufficient concentrations, it did result in reduced levels of T and increased levels of LH [3, 11–13].

An alternative mechanism is the role of the hormone inhibin in the feedback loop. Inhibin is secreted by the prostate gland. One might speculate that inhibin produced by the prostate produces a feedback action on the H-P Axis and contributes to the LH and FSH rise [6, 7, 14–16]. Experimental animal models of prostatectomies showed clear increase in the FSH but not the LH. To date there is no clear understanding of whether a decrease in inhibin levels may stimulate these hormonal findings.
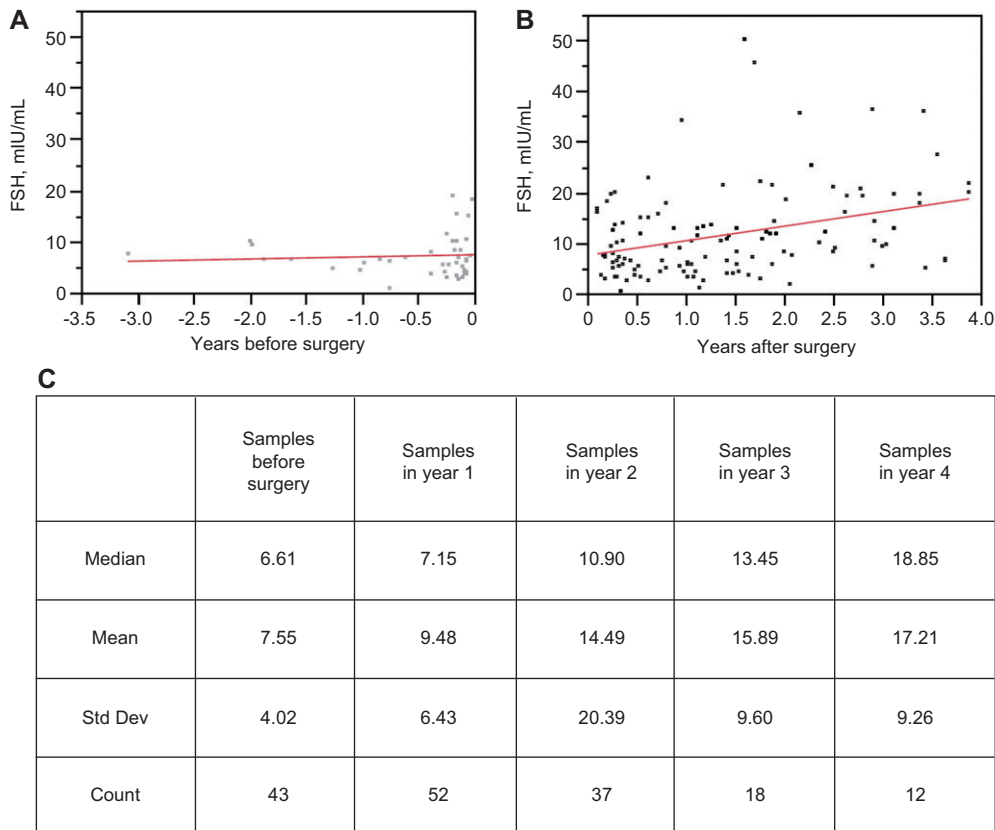
Figure 6 FSH (m/IU/mL) before and after cryosurgery.
Panel A, linear fit using observations after cryosurgery; slope, 0.414 units per year, p=0.651. Panel B, linear fit using observations after cryosurgery; slope, 2.863 units per year, p=0.0002. Panel C, median and mean FSH samples before surgery and each year after surgery, 1, 2, 3, 4th year.

In animal tumor growth models, inhibin is known to suppress both Dunning R3327G androgen-dependent and androgen-independent cell lines [17, 18]. A recent publication by Lachner showed that inhibin was not the causal factor for the testosterone changes in patients with prostate cancer [8].

Madersbacher et al. [7] compared hormone changes for large volume radical prostatectomies to smaller volume ablation by transurethral resection of the prostate and leaving the peripheral zone intact. Hormone measurement included total and free testosterone, LH, FSH, SHBG and serum blood samples were obtained immediately before surgery, at 6 months and up to 12 months after surgery. Aside from the study arm of 49 patients in the radical prostatectomy arm and 51 patients in the transurethral prostatectomy arm, they added a third arm of 46 patients as 'watchful waiting' controls. In the radical prostatectomy of large volume prostate gland arm of the study, there was a significant increase in the LH and FSH, whereas the transurethral prostatectomy and the control arm group did not show any changes in the LH and FSH.

This study suggests that the LH and FSH changes may be dependent on the amount of prostate tissues volume destroyed [7]. However others noted LH increases even with a transurethral resection of the prostate [19].

The elevated LH levels noted in this study are analogous with that noted in the compensated hypogonadism reported previously [20]. Compensated hypogonadism is thought to be prevalent in men with comorbidities and is associated predominantly with physical symptoms [20]. Because T levels vary significantly among individuals, it is likely that a small decline in T in some of these individuals from previously normal to current low normal levels may contribute to the observed increase in LH and FSH. As suggested by Tajar et al. [20], higher levels of LH may indicate a decline in T levels within the normal range, eliciting a feedback mechanism in the HPA with concomitant increase in LH and FSH.

Our data supports the observation that LH and FSH rise after prostate removal or ablation and those increases are persistent up to 3 years after surgical resection or ablation of the entire gland. The first year after cryosurgery showed

the most dramatic increases but the second and third year did not show further increases as noted in Table 1.

The strengths of our study are the longitudinal design and the measurements of circulating plasma hormone levels 3 years before surgery and 3 years after surgical cryoablation. This long time period reduces the confounding factors normally associated with short periods before or after surgery because hormonal changes are often altered by stress and anxiety of undergoing surgery and recovery from surgery.

The limitation of this study is the small number of cases identified for study. Additionally, theses were consecutive cases with no randomization in the design. A controlled matched group study would have been ideal but difficult to assemble in an outpatient clinic setting.

With larger numbers of subjects for study, future designs must adjust for confounding variables such as BMI, weight, age, diabetes, and renal failure, to truly validate whether the prostate participates in the feed-back and feed-forward loop of the hypothalamic-pituitary axis. To test for significance, multiple center studies may be necessary to combine sufficient data in a meta-analysis review.

A second limitation of this study is that ablation of the prostate by cryosurgery of the total gland is not representative of other more common prostate surgical procedures for prostate cancer, although we suspect that this finding will persist because others have already reported similar findings after open surgery. We suspect the same changes occur with brachytherapy and external beam radiation treatment modalities.

As radical prostatectomy is still the most common operation in urology today, the centers with a large surgical volume with an additional radiation program to treat prostate cancers could generate larger meaningful results for study.

Conclusion

Our findings, together with those observed in other human and animal studies, support the hypothesis that the prostate is an endocrine gland and produces biochemical factors that have the ability to modulate the H-P Axis and regulate levels of LH and FSH.

References

1. Miller LR, Partin AW, Chan DW, Bruzek DJ, Dobs, AS, Epstein JI, Walsh PC. Influence of radical prostatectomy on serum hormone levels. J Urol 1998;160:449.

2. Olsson M, Ekstrom L, Schulze J, Kjellman A, Akre O, Rane A, Gustafsson O. Radical prostatectomy: influence on serum and urinary androgen levels. Prostate 2010;70:200–5.

3. Bantis A, Zissimopoulos A, Athanasiadou P, Gonidi M, Agelonidou E, Strataki A, Matthaios D, Tsartsarakis A. [Serum testosterone, dihydrotestosterone, luteinizing hormone and follicle-stimulating hormone versus prostate specific antigen in patients with localized prostate adenocarcinoma who underwent radical prostatectomy. Radioimmunoassays measurements]. Hell J Nuc Med 2007;10:56–61.

4. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward "two-disease" theory. Prostate 1982;3:
579–88.

5. Robinson MR, Thomas BS. Effect of hormonal therapy on plasma testosterone levels in prostatic carcinoma. Br Med J 1971;
4:391.

6. Schatzl G, Madersbacher S, Thurridl T, Waldmuller J, Kramer G, Haite A, Marberger M. High-grade prostate cancer is associated with low serum testosterone levels. Prostate 2001;47:52–8.

7. Madersbacher S, Schatzl G, Bieglmayer C, Reiter WJ, Gassner C, Berger P, Zidek T, Marberger M. Impact of radical prostatectomy and TURP on the hypothalamic-pituitary-gonadal hormone axis. Urology 2002;60:869–74.

8. Lachner KE, Maerk I, Koller A, Bieglmayer C, Marberger M, Kratzik C, Schatzl G. Serum inhibin – not a cause of low testosterone levels in hypogonadal prostate cancer? Urology 2008;72:1121–4.

9. Lane BR, Stephenson AJ, Magi-Galluzzi C, Lakin MM, Klein EA. Low testosterone and risk of biochemical recurrence and poorly differentiated prostate cancer at radical prostatectomy. Urology 2008;72:1240–5.

10. Schaison G, Renoir M, Lagoguey M, Mowszowicz I. On the role of dihydrotestosterone in regulating luteinizing hormone secretion in man. J Clin Endocrinol Metab 1980;51:1133–7.

11. Page ST, Lin DW, Mostaghel EA, Marck BT, Wright JL, Wu J, Amory JK, Nelson PS, Matsumoto AM. Dihydrotestosterone administration does not increase intraprostatic androgen concentrations or alter prostate androgen action in healthy men: a randomized-controlled trial. J Clin Endocrinol Metab 2011;96:430–7.

12. Idan A, Griffiths KA, Harwood DT, Seibel MJ, Turner L, Conway AJ, Handelsman DJ. Long-term effects of dihydrotestosterone treatment on prostate growth in healthy, middle-aged men

without prostate disease: a randomized, placebo-controlled trial. Ann Intern Med 2010;153:621–32.

13. Abbott DH, Batty KA, Dubey AK, Herbert J, Shiers HM. The passage of 5 alpha-dihydrotestosterone from serum into cerebrospinal fluid and LH negative feedback in castrated rhesus monkeys. J Endocrinol 1985;104:325–30.

14. Phadke M, Vanage GR, Sheth AR. Circulating levels of inhibin, prolactin, TSH, LH and FSH in benign prostatic hypertrophy before and after tumor resection. Prostate 1987;10:115–22.

15. Lukkarinen O. Total and SHBG-bound testosterone and 5 alpha-dihydrotestosterone serum concentrations in normal elderly men and patients with benign prostatic hypertrophy before and after removal of the adenoma. Br J Urol 1980;52: 377–80.

16. Lukkarinen O, Hammond GL, Kontturi M, Vihko R. Peripheral and prostatic vein steroid concentrations in benign prostatic hypertrophy patients before and after removal of the adenoma. Scand J Urol Nephrol 1980;14:225–7.

17. Ying S-Y, Zhang Z, Huang G. Expression and localization of inhibin/activin subunits and activin receptors in the normal rat prostate. Life Sci 1997;60:397–401.

18. Lokeshwar BL, Hurkadli KS, Sheth AR, Block NL. Human prostatic inhibin suppresses tumor growth and inhibits clonogenic cell survival of a model prostatic adenocarcinoma, the Dunning R3327G rat tumor. Cancer Res 1993;53: 4855–9.

19. Sasagawa I, Nakada T, Suzuki H, Adachi Y, Adachi M. Effect of transurethral resection of prostate on plasma hormone levels in benign prostatic hyperplasia. Br J Urol 1993;72:611–4.

20. Tajar A, Forti G, O'Neill TW, Lee DM, Silman AJ, Finn JD, Bartfai G, Boonen S, Casanueva FF, Giwercman A, Han TS, Kula K, Labrie F, Lean ME, Pendleton N, Punab M, Vanderschueren D, Huhtaniemi IT, Wu FC; EMAS Group. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. J Clin Endocrinol Metab 2010;95:1810–8.