KJU
Korean Journal of Urology

www.kjurology.org
http://dx.doi.org/10.4111/kju.2012.53.1.9

Urological Oncology

Usefulness of Preoperative Serum Testosterone as a Predictor of Extraprostatic Extension and Biochemical Recurrence

Hyoung Jong Kim, Byung Hoon Kim, Chol Hee Park, Chun Il Kim

Department of Urology, Keimyung University School of Medicine, Daegu, Korea

Purpose: A great variety of studies on preoperative serum testosterone as a predictor of progression of prostate cancer have been reported recently. The purpose of this study was to investigate the relationship of preoperative serum testosterone levels in patients who underwent radical prostatectomy with prognostic factors.

Materials and Methods: Clinical data were collected from 60 patients who underwent radical prostatectomy. The 60 cases were divided into 2 groups according to their preoperative serum testosterone levels: group 1 (n=21), <3 ng/ml; group 2 (n=39), ≥ 3 ng/ml. The groups were compared according to prog-ression factors. Multivariate logistic regression analysis was performed to determine the correlation between biochemical recurrence and each variable.

Results: The incidence of extraprostatic invasions was significantly higher in group 1 with 13 cases in group 1 (61.9%) and 11 cases in group 2 (28.2%) (p=0.011). The incidence of biochemical recurrence was also significantly higher in group 1 with 5 cases in group 1 (23.8%) and 2 cases in group 2 (5.1%) (p=0.032). A low serum testosterone level (≤ 3 ng/ml) was associated with an increased risk of biochemical recurrence (odds ratio [OR], 13.64; 95% confidence interval [CI], 1.66 to 2.43; p=0.015) and an increased risk of extraprostatic invasions (OR, 4.96; 95% CI, 1.41 to 17.38; p=0.012).

Conclusions: The incidence rates of extraprostatic invasions and biochemical recurrence were significantly higher in the group with preoperative average serum testosterone of less than 3 ng/ml. Therefore, these results suggest that preoperative average serum testosterone will be useful in predicting postoperative prostate cancer progression.

Key Words: *Disease progression; Prostatic neoplasms; Testosterone*

Article History:
received 7 March, 2011
accepted 27 September, 2011

Corresponding Author:
Chun Il Kim
Department of Urology, Dongsan Medical Center, Keimyung University School of Medicine, 194, Dongsan-dong, Jung-gu, Daegu 700-712, Korea
TEL: +82-53-250-7646
FAX: +82-53-250-7643
E-mail: cikim@dsmc.or.kr

INTRODUCTION

Androgen is known to not only play essential roles in the growth and maintenance of the prostate but also be involved in the growth of prostate cancer cells [1]. Through animal experiments, Lucia et al. [2] found that prostate cancer is suppressed when androgen values in the body are reduced. In addition, many studies are currently being conducted to compare diverse stages of prostate cancer progression and related prognosis with androgen values [3]. It is known that preoperative average serum testosterone is associated with low rates of responses to treatment and poorer progression in metastatic prostate cancer and that, in particular, a preoperative average serum testosterone level of 3 ng/ml or less is associated with short survival time and advanced disease [4]. Currently, although clinical stages, Gleason scores obtained from biopsies, and prostate-specific antigen (PSA) values are known to be markers for predicting post-radical-prostatectomy progression, the relationship between preoperative average serum testosterone and prognoses has not yet been clearly established. In this respect, we intended to examine the relationship between preoperative average serum testosterone and post-radical-prostatectomy prostate cancer progression in

patients who had undergone a radical prostatectomy.

MATERIALS AND METHODS

The subjects of this study were 60 patients in whom preoperative average serum testosterone was measured among 81 patients who were diagnosed with prostate cancer between January 2005 and December 2009 and underwent a radical prostatectomy as the initial treatment. The average age of the patients was 65 years, the mean follow-up period was 18 months (range, 2 to 48 months), and the preoperative average PSA was 9.48 ng/ml.

According to hospital records, the patients' ages, body mass index (BMI), preoperative PSA, Gleason scores, prostate volumes, extraprostatic invasions, seminal vesical invasions, positive surgical margins, lymphovascular invasions, perineural invasions, biochemical recurrence (BCR), and metastatic states were examined. Blood for measuring preoperative serum testosterone was collected in the morning when testosterone values are high and stable, and the values were measured by radioimmunoassay. BCR was defined as cases in which PSA measured 0.2 ng/ml or higher two times successively after the surgery. The 12 core biopsy scheme used in our institution includes a standard sextant, which was originally described by Hodge et al. [5], as well as a lateral sextant scheme (lateral apex, lateral mid-gland, lateral base) [6]. The biopsy policy of our institution consists of an additional two core biopsies in cases of palpable nodules in the digital rectal examination or suspicious lesions in transrectal ultrasonography (TRUS). Biopsies were performed under ultrasound guidance by use of an 18 gauge, 2 cm, Trucut core needle biopsy, and pathological judgments of all tissues were made by two pathology boards. TRUS-guided prostate biopsy was performed to assess individual biopsy cores for any existence of tumors and Gleason scores, and postoperative biopsies were performed to assess extraprostatic invasions, seminal vesical invasions, positive surgical margins, lymphovascular invasions, and perineural invasions.

On the basis of a testosterone value of 3 ng/ml, the patients were divided into two groups [7,8]: 21 cases with preoperative average serum testosterone of less than 3 ng/ml (35%), who were defined as group 1, and 39 cases with preoperative average serum testosterone of 3 ng/ml or more (65%), who were defined as group 2. Ages, BMI, Gleason scores, prostate volumes, extraprostatic invasions, seminal vesical invasions, positive surgical margins, lymphovascular invasions, perineural invasions, BCR, and the existence of metastatic tumors were compared between the two groups.

Statistical analyses were performed by using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Chi-square tests and student's t-tests were used to identify statistical differences between the two groups and multivariate logistic regression analysis was performed to determine the correlation between biochemical recurrence and each variable. In all analyses, cases in which $p < 0.05$ were considered to be statistically significant.

TABLE 1. Baseline characteristics of the study subjects

Characteristic	Value
Age (yr)	65.1 (52-74)
BMI (kg/m^2)	23.4 (18-24)
PSA	9.48 (2.45-20.3)
Clinical stage	
T1c (%)	27 (45.0)
T2a (%)	15 (25.0)
T2b (%)	9 (15.0)
T2c (%)	8 (13.3)
T3 (%)	1 (1.6)
Gleason score	
≤6 (%)	29 (48.3)
7	20 (33.3)
≥8 (%)	11 (18.3)
Prostate volume (m/l) (range)	37.7 (14-87)

Values are presented as mean±SD or number (%).
BMI, body mass index; PSA, prostate-specific antigen.

RESULTS

1. Patient characteristics

The patients' mean age was 65.1 years (range, 52 to 74 years), their mean BMI was 23.4 kg/m^2 (range, 18 to 24 kg/m^2), and their mean PSA was 9.48 ng/ml (range, 2.45 to 20.3 ng/ml). The patients' clinical stages included 27 cases of T1c (45%), 15 cases of T2a (25%), 9 cases of T2b (15%), 8 cases of T2c (13.3%), and 1 case of T3 (1.6%). Gleason scores obtained from biopsies included 29 cases of a Gleason score of 6 (48.3%), 20 cases of a score of 7 (33.3%), and 11 cases of scores of 8 to 10 (18.3%), and the average prostatic volume was 37.7 ml (range, 16 to 87 ml) (Table 1).

2. Comparison of clinicopathologic features according to preoperative serum testosterone level

The values of average preoperative serum testosterone in group 1 and group 2 were 1.99 ng/ml and 5.02 ng/ml, respectively, whereas no significant differences (p=0.628) were shown in the groups' respective average ages of 66 and 64 years (p=0.782) or BMI of 25.2 kg/m^2 and 25.5 kg/m^2. Mean PSA values were higher in group 1, 10.45 ng/ml in group 1 and 7.67 ng/ml in group 2 (p=0.031), whereas there was no significant difference in Gleason scores or average prostatic volumes between the two groups (p=0.726, p=0.793). The incidence of extraprostatic invasion was significantly higher in group 1, 13 cases in group 1 (61.9%) and 11 cases in group 2 (28.2%) (p=0.011), whereas there were no significant differences between the two groups in positive surgical margins, lymphovascular invasions, perineural invasions, or seminal vesical invasions. The incidence of BCR was higher in group 1, 5 cases in group 1 (23.8%) and 2 cases in group 2 (5.1%) (p=0.032), whereas there were no significant differences in metastasis between the two groups, with 1 case each in each group (4.7%,

TABLE 2. Comparison of clinicopathologic features according to preoperative serum testosterone level

Variable	Group 1 (n=21)	Group 2 (n=39)	p-value
Age (yr)	66.71±5.6	64.23±5.9	0.782[a]
BMI (kg/m^2)	25.29±2.1	22.59±2.0	0.628[a]
Pretreatment PSA (ng/ml)	10.45±6.1	7.67±4.0	0.031[a]
Prostate volume (ml)	40.55±17.7	36.33±17.0	0.793[a]
Gleason score	7.33±1.1	7.21±1.1	0.726[a]
Biochemical recurrence (%)	5 (23.2)	2 (5.1)	0.032[b]
Extraprostatic extension (%)	13 (61.9)	11 (28.2)	0.011[b]
Positive margin (%)	2 (9.5)	2 (5.1)	0.515[b]
Lymphovascular invasion (%)	4 (19)	3 (7.6)	0.191[b]
Perineural invasion (%)	8 (38)	10 (25)	0.315[b]
Distant metastasis (%)	1 (4.7)	1 (2.5)	0.651[b]

Values are presented as mean±SD or number (%). Group 1: preoperative serum testosterone <3 ng/ml, group 2: preoperative serum testosterone ≥ 3 ng/ml.
BMI, body mass index; PSA, prostate-specific antigen.
[a]: Student's t-test was applied for comparison of continuous variables, [b]: The Pearson chi-square test and Fisher exact test were used to compare categorical variables.

TABLE 3. Logistic regression analysis of the correlation between biochemical recurrence and each variable

Variables	Odds ratio	95.0% CI	p-value
Age (yr)	0.836	0.706-1.989	0.057
Pretreatment PSA (ng/ml)	0.845	0.571-1.250	0.399
Gleason score	0.829	0.370-1.861	0.650
Preoperative testosterone (≤ 3 ng/ml)	13.649	1.661-2.431	0.015

PSA, prostate-specific antigen; CI, confidence interval.

TABLE 4. Logistic regression analysis of the correlation between extraprostatic invasion and each variable

Variables	Odds ratio	95.0% CI	p-value
Age (yr)	0.988	0.896-1.090	0.816
Pretreatment PSA (ng/ml)	0.853	0.684-1.062	0.155
Gleason score	1.325	0.781-2.248	0.297
Preoperative testosterone (≤ 3 ng/ml)	4.965	1.418-17.384	0.012

PSA, prostate-specific antigen; CI, confidence interval.

2.5%) (Table 2).

3. Correlation between biochemical recurrence and each variable

A low serum testosterone level (≤ 3 ng/ml) was associated with an increased risk of biochemical recurrence (odds ratio [OR], 13.64; 95% confidence interval [CI], 1.66 to 2.43; p=0.015). The patients' ages, preoperative PSA, and Gleason scores did not have a significant association with increased risk of biochemical recurrence ($p>0.05$) (Table 3).

4. Correlation between extraprostatic invasion and each variable

A low serum testosterone level (≤ 3 ng/ml) was associated with an increased risk of extraprostatic invasions (OR, 4.96; 95% CI, 1.41 to 17.38; p=0.012). The patients' ages, preoperative PSA, and Gleason scores did not have a significant association with an increased risk of extraprostatic invasions ($p>0.05$) (Table 4).

DISCUSSION

In males, 90% of testosterone is generated in Leydig cells in the testes and the remaining 10% in the adrenal glands [9]. This testosterone is converted into the form of di-hydro-testosterone (DHT). DHT works through androgen receptors to promote the growth of the prostate and plays important roles in the growth of male reproductive tissues in the testes and the prostate [10].

Since the first report of a relationship between serum testosterone and prostate cancer in 1941, many related studies have been conducted [11]. Adlercreutz et al. [12] found that the higher the value of mean serum testosterone, the better patients' responses to hormone therapy in prostate cancer for the first time, and Chodak et al. [4] and Chen et al. [13] reported that patients with low preoperative testosterone showed poorer prognosis than did those with normal values and showed poorer responses to treatment.

With regard to serum testosterone and prostate cancer stages, Massengill et al. [14] found that preoperative testosterone was lower in advanced localized prostate cancer (T3-4N0M0) cases than in localized prostate cancer (pT2) cases and suggested that low preoperative testosterone in localized prostate cancer was a predictive factor for extraprostatic invasions. In the results of the present study also, 28.2% of the high preoperative testosterone group showed extraprostatic invasions, whereas 61.9% of the low preoperative testosterone group showed extraprostatic invasions, which was a statistically significant difference between the two groups.

Teloken et al. [15] reported that low preoperative testosterone was associated with positive surgical margins, but their study involved short follow-up periods and was conducted with a small number of patients. In the present study also, there was no significant difference in positive surgical margins between the two groups. However, because surgical margins are greatly affected by surgical skills and surgeons' experience, it is likely that simple comparison of these results is not very meaningful. Furthermore, Yamamoto et al. [16] examined the relationship between preoperative testosterone and lymphovascular invasions, perineural invasions, and seminal vesical invasions in 272 patients who underwent a radical prostatectomy and reported that there was no particular association. No association was found in the present study either.

Yamamoto et al. [16] reported that BCR was more frequent in patients with low preoperative testosterone. However, Zhang et al. [17] reported that low preoperative testosterone was not associated with BCR in patients who underwent a radical prostatectomy, and the reason proposed by those authors was that this study included many patients with locally advanced BCR. In the present study, BCR was more frequent in patients with low preoperative testosterone (23.8% vs. 5.1%).

Hoffman et al. [7] suggested that low preoperative testosterone was a predictive factor for high Gleason scores, and Schatzl et al. [18] reported high associations between low preoperative testosterone and high Gleason scores. However, Massengill et al. [14] examined 879 patients who underwent a radical prostatectomy and reported that low preoperative testosterone values were not associated with Gleason scores. The results of the present study also showed no correlation between preoperative testosterone values and Gleason scores.

It is generally known that normal prostates produce protein materials such as PSA thanks to differentiated actions of androgen [19]. Morgentaler [20] suggested that testosterone values were low in hypogonadism patients and that the possibility of prostate cancer would be high if PSA values were 4.0 ng/ml or lower. Koo and Shim [21] examined 120 patients with a PSA value of 10.0 ng/ml or higher who underwent a transrectal biopsy and reported that testosterone values at diagnosis were not associated with enhanced PSA values. In the present study, however, PSA values were higher in the group with low preoperative testosterone (10.45 ng/ml vs 7.67 ng/ml). This is considered to be because the number of subjects was small; thus, additional studies will be necessary.

Many hypotheses are being reported in relation to the mechanisms related to serum testosterone values, disease progression, and prognosis. There are hypotheses that regard changes in testosterone values simply as secondary changes in chronic disease or disease progression and hypotheses that regard changes in testosterone values as negative feedback from the hypothalamic-pituitary-gonadal hormone axis. Miller et al. [22] found that postoperative testosterone values increased in patients who underwent a prostatectomy and suggested that this indicated the presence of substances corresponding to negative feedback in prostate cancer cells. Currently, inhibin is considered to be a substance involved in this negative feedback mechanism through the hypothalamic-pituitary-gonadal hormone axis. Risbridger et al. [23] reported that higher inhibin values were associated with higher risks of biochemical recurrences in 174 patients who underwent a radical prostatectomy due to prostate cancer. In animal experimental models, it was shown that inhibin was generated in the testis to suppress prostate and hypothalamic-pituitary secretions [24,25]. Thus far, studies of inhibin have been limited to animal experiments and thus the roles of inhibin in human prostates are not yet clear.

Large parts of the relationship between prostate cancer and testosterone are also not yet known. Freedland et al. [26] suggested that because serum testosterone does not affect prostatic testosterone, it is impossible to predict the prognoses of prostate cancer with just the level of serum testosterone, and Marks et al. [27] suggested that therapeutic testosterone administration in hypogonadism patients would not affect prostatic testosterone. Furthermore, there is a report that if finasteride, a 5a-reductase inhibitor, is used, although the overall incidence of prostate cancer will be reduced, the lowered prostatic testosterone will promote the growth of high-grade prostate cancer that is less affected by androgen and thus increase the risk of onset of high-grade prostate cancer [28,29]. Large-scale studies on a large number of patients will be necessary to clarify the relationship between testosterone and prostate cancer.

CONCLUSIONS

The incidence rates of extraprostatic invasions and biochemical recurrences were significantly higher in the group with preoperative serum testosterone levels less than 3 ng/ml Therefore, these results suggest that preoperative serum testosterone measurement will be helpful in predicting postoperative prostate cancer progression.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. Cancer Res 1999;59:1461-4.
2. Lucia MS, Bostwick DG, Bosland M, Cockett AT, Knapp DW, Leav I, et al. Workgroup I: rodent models of prostate cancer. Prostate 1998;36:49-55.
3. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and younger age predict for a poor outcome in metastatic prostate cancer. Am J Clin Oncol 1997;20:605-8.
4. Chodak GW, Vogelzang NJ, Caplan RJ, Soloway M, Smith JA. Independent prognostic factors in patients with metastatic (stage D2) prostate cancer. The Zoladex Study Group. JAMA 1991;265:618-21.

5. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol 1989;142:71-4.
6. Presti JC Jr, O'Dowd GJ, Miller MC, Mattu R, Veltri RW. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. J Urol 2003;169:125-9.
7. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a maker for high grade prostate cancer? J Urol 2000;163:824-7.
8. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice gulidline. J Clin Endocrinol Metab 2010;95:2536-59.
9. Carson C 3rd, Rittmaster R. The role of dihydrotestosterone in benign prostatic hyperplasia. Urology 2003;61(4 Suppl 1):2-7.
10. Heemers HV, Tindall DJ. Androgen receptor (AR) coregulators: a diversity of functions converging on and regulating the AR transcriptional complex. Endor Rev 2007;28:778-808.
11. Huggins C, Stevens RE Jr, Hodges CV. Stduies on prostate cancer: II .The effect of castration on advanced carcinonma of the prostate gland. Arch Surg 1941;43:209-23.
12. Adlercreutz H, Rannikko S, Kairento AL, Karonen SL. Hormonal pattern in prostate cancer. II. Correlation with primary response to endocrine treatment. Acta Endocrinol (Copenh) 1981;98: 634-40.
13. Chen SS, Chen KK, Lin AT, Chang YH, Wu HH, Chang LS. The correlation between pretreatment serum hormone levels and treatment outcome for patients with prostatic cancer and bony metastasis. BJU Int 2002;89:710-3.
14. Massengill JC, Sun L, Moul JW, Wu H, McLeod DG, Amling C, et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. J Urol 2003;169:1670-5.
15. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. J Urol 2005;174:2178-80.
16. Yamamoto S, Yonese J, Kawakami S, Ohkubo Y, Tatokoro M, Komai Y, et al. Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy. Eur Urol 2007;53:696-701.
17. Zhang PL, Rosen S, Veeramachaneni R, Kao J, DeWolf WC, Bubley G. Association between prostate cancer and serum testosterone levels. Prostate 2002;53:179-82.
18. Schatzl G, Madersbacher S, Thurridl T, Waldmüller J, Kramer G, Haitel A, et al. High-grade prostate cancer is associated with lower serum testosterone levels. Prostate 2001;47:52-8.
19. Schalken JA. Molecular aspects of hormone-independent prostate cancer. BJU Int 2007;100(Suppl 2):52-5.
20. Morgentaler A. Testosterone and prostate cancer: an historical perspective on modern myth. Eur Urol 2006;50:935-9.
21. Koo JM, Shim BS. Significance of serum testosterone for prostate-specific antigen (PSA) elevation and prediction of prostate cancer in patients with PSA above 10 ng/ml. Korean J Urol 2010;51:831-5.
22. Miller LR, Partin AW, Chan DW, Bruzek DJ, Dobs AS, Epstein JI, et al. Influence of radical prostatectomy on serum hormone levels. J Urol 1998;160:449-53.
23. Risbridger GP. Thomas T, Gurusinghe CJ, McFarlane JR. Inhibin-related proteins in rat prostate. J Endocrinol 1996; 149:93-9.
24. Lokeshwar BL, Hurkadli KS, Sheth AR, Block NL. Human prostatic inhibin suppresses tumor growth and inhibits clonogenic cell survival of model prostatic adenocarcinoma, the Dunning R3327G rat tumor. Cancer Res 1993;53:4855-9.
25. Sheth AR, Grade SV, Mehta MK, Shah MG. Hormonal modulation of biosynthesis of prostatatic specific antigen, prostate specific acid phosphatase and prostate inhibin peptide. Indian J Exp Biol 1992;30:157-61.
26. Freedland SJ, Isaacs WB, Platz EA, Terris MK, Aronson WJ, Amling CL, et al. Prostate size and risk high-grade, advanced prostate cancer and biochmical progression after radical prostatectomy: a search database study. J Chin Oncol 2005;23;7546-54.
27. Marks LS, Mazer NA, Mostaghel E, Hess DL, Dorey FJ, Epstein JI, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA 2006;296:2351-61.
28. Scardino PT. The prevention of prostate cancer-the dilemma continues. N Engl J Med 2003;349:297-9.
29. Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA 1996; 276:1904-6.