

Urological Oncology

Hospitalization Decreases Serum Prostate-Specific Antigen Values Compared With Outpatient Values in Patients With Benign Prostatic Diseases

In Seok Yoon, Tae Young Shin¹, Sun Il Kim, Seong Kon Park, Hyun Ik Jang, Jong Bo Choi, Hyun Soo Ahn, Young Soo Kim, Se Joong Kim

Department of Urology, Ajou University School of Medicine, Suwon, ¹Department of Urology, Hallym University College of Medicine, Chuncheon, Korea

Purpose: To investigate whether hospitalization influences serum prostate-specific antigen (PSA) values.

Materials and Methods: Transrectal ultrasound-guided prostate biopsies were performed for detecting prostate cancer in 2,017 patients between February 2001 and April 2011 at Ajou University Hospital. Of those patients, 416 patients who were hospitalized for prostate biopsies, whose serum PSA values were measured at the outpatient department within 1 month of admission and also just after admission, and who had negative prostate biopsy results were included in the present study. We retrospectively reviewed the data of the 416 patients and compared the serum PSA values measured in the outpatient department with those measured during hospitalization.

Results: Among all 416 patients, the interval between the two PSA measurements was 22.2 days (range, 3 to 30 days) and the prostate size measured by transrectal ultrasonography was 53.63 mL (range, 12.8 to 197.9 mL). Among all patients, mean serum PSA levels measured during hospitalization were significantly lower than those measured in the outpatient department (6.69 ng/mL vs. 8.01 ng/mL, $p < 0.001$). When stratified according to age, the presence or absence of chronic prostatitis in the biopsy pathology, serum PSA levels, and prostate size, the serum PSA levels measured during hospitalization were significantly lower than those measured in the outpatient department in all subgroups, except in cases aged 20 to 39 years and those with PSA < 4 ng/mL, in whom no significant differences were shown.

Conclusions: Hospitalization decreases serum PSA values compared with those measured on an outpatient basis in patients with benign prostatic diseases. Therefore, serum PSA values should be checked on an outpatient basis for serial monitoring.

Keywords: Hospital outpatient clinics; Hospitalization; Prostate-specific antigen

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Article History:

received 10 April, 2013
accepted 27 June, 2013

Corresponding Author:

Se Joong Kim
Department of Urology, Ajou
University School of Medicine,
206 World cup-ro, Yeongtong-gu,
Suwon 443-721, Korea
TEL: +82-31-219-5272
FAX: +82-31-219-5276
E-mail: sejoong@ajou.ac.kr

INTRODUCTION

Prostate cancer is the most common cancer in men in the United States and the fifth most common cancer in men in Korea [1,2]. Prostate-specific antigen (PSA) is one of the most important tools for the early detection of prostate cancer. An elevated serum PSA level is an indication to pur-

sue additional diagnostic evaluation, including ultrasound-guided prostate biopsies, to rule out prostate cancer [3,4].

However, the major drawback of serum PSA testing is that PSA is prostate-specific but not prostate-cancer-specific. Various physiological and benign pathologic processes, including prostatitis, urinary retention, and ejacu-

lation, can affect the serum PSA level [3-8]. Also, there are limited data on the effect of hospitalization on the serum PSA level. Serum PSA levels measured at least 24 hours after admission in hospitalized patients have been shown to be decreased compared with those measured in the outpatient department before admission, which suggests that the lack of activity associated with bed rest during hospitalization might decrease serum PSA values [9,10]. However, there have been no reports comparing serum PSA levels measured just after admission with those measured in the outpatient department before admission. If serum PSA levels measured just after admission are decreased compared with those measured in the outpatient department, only the serum PSA levels measured in the outpatient department should be considered for the serial monitoring of PSA levels in patients with equivocal serum PSA values. Therefore, in this study, inpatient serum PSA (IPsPSA) values measured just after admission were compared with the preadmission outpatient serum PSA (OPsPSA) values to investigate whether hospitalization influences serum PSA values.

MATERIALS AND METHODS

Transrectal ultrasound-guided needle biopsies of the prostate were performed for detecting prostate cancer in 2,017 patients between February 2001 and April 2011 at our institution. The indications for prostate biopsy were serum PSA elevation or abnormal findings on a digital rectal examination or transrectal ultrasonography. Young patients with serum PSA elevation usually underwent prostatitis workup and were given oral antibiotic treatment if needed. The decision to biopsy was based on an elevated repeat PSA level after a period of time and the patient's preference despite being informed of the low risk of prostate cancer. Among the total 2,017 patients, the patients who underwent prostate biopsies on an outpatient department basis, in whom preadmission OPsPSA was not measured at Ajou University Hospital, who had a pathologic diagnosis of prostate cancer, who had recent clinical evidence of acute urinary retention, or who had an interval of more than 1 month between OPsPSA and IPsPSA were excluded. Patients who had been taking 5 α -reductase inhibitors or phytotherapeutic agents within 6 months of biopsy were also excluded from the analysis. All other medications including α -blockers were allowed to be taken until the day of biopsy, except for antiplatelet drugs and anticoagulants, which were instructed to be stopped or switched to short-acting drugs a few days before. Finally, we retrospectively reviewed the data of 416 patients who were hospitalized for prostate biopsies; whose OPsPSA and IPsPSA values were measured in our hospital within 1 month of admission and just after admission, respectively; and whose prostate biopsy results revealed no evidence of cancer.

Blood sampling for PSA was always instructed to be taken before any procedures that could influence the serum PSA level, such as digital rectal examination, prostatic

massages, transrectal ultrasonography, and cystoscopy. No fasting was required before the blood sampling for PSA. Five milliliters of blood was collected from an antecubital vein and was immediately sent to our hospital's central laboratory. The sample was processed without delay and was analyzed within 2 hours of collection. PSA was measured in serum samples by using a microparticle enzyme immunoassay in an A \times SYM immunoassay analyzer (Abbott Diagnostics, Abbott Park, IL, USA) until 2006 and afterwards by using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) in a Modular E170 analyzer (Hitachi, Ibaraki, Japan).

The patients were usually hospitalized at 17:00 to 18:00 in the afternoon for prostate biopsies. Samples were obtained for blood tests, including PSA, immediately after admission, and prostate biopsies were performed the next day after admission, irrespective of the serum PSA level during hospitalization.

The OPsPSA and IPsPSA measurements were compared according to age, the presence or absence of chronic prostatitis in biopsy pathology, serum PSA levels, and prostate size. Statistical analysis was performed by using paired sample t-tests with SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered to be statistically significant in all of the analyses.

RESULTS

The mean age of the 416 patients included in this study was 61.6 years (range, 29 to 85 years). Among all 416 patients, the mean interval between OPsPSA and IPsPSA measurements was 22.2 days (range, 3 to 30 days). The mean prostate size measured by transrectal ultrasonography was 53.63 mL (range, 12.8 to 197.9 mL).

Among all 416 patients, the mean IPsPSA levels (6.69 ng/mL) were significantly lower than the OPsPSA levels (8.01 ng/mL, $p < 0.001$) (Table 1). When the patients were stratified according to age, mean IPsPSA levels were significantly lower than OPsPSA levels in patients aged 40 to 59 years ($p < 0.001$) and ≥ 60 years ($p < 0.001$). The mean IPsPSA levels were lower than OPsPSA levels in patients aged 20 to 39 years, but not significantly so ($p=0.141$). When the patients were stratified according to the presence or absence of chronic prostatitis in biopsy pathology, mean IPsPSA levels were significantly lower than OPsPSA levels, irrespective of the presence or absence of chronic prostatitis ($p < 0.001$ and $p=0.001$, respectively). When the patients were stratified according to the serum PSA level, mean IPsPSA levels were significantly lower than OPsPSA levels in patients with PSA of 4 to 9.9 ng/mL ($p < 0.001$) and ≥ 10 ng/mL ($p < 0.001$). The mean IPsPSA levels were lower than the OPsPSA levels in patients with PSA < 4 ng/mL, but not significantly so ($p=0.116$). When the patients were stratified according to prostate size, mean IPsPSA levels were significantly lower than OPsPSA levels, irrespective of prostate size (Table 1).

TABLE 1. Comparison of serum PSA levels measured in the outpatient department and those measured during hospitalization

| Variable | No. | PSA level (ng/mL) | | p-value |
|---|-----|--------------------------|------------------------|---------|
| | | At outpatient department | During hospitalization | |
| Patient | 416 | 8.01±6.39 | 6.69±4.98 | < 0.001 |
| Age (y) | | | | |
| 20-39 | 24 | 7.35±2.16 | 7.06±2.01 | 0.141 |
| 40-59 | 126 | 7.61±7.05 | 6.23±5.64 | < 0.001 |
| ≥60 | 266 | 8.26±6.33 | 6.88±4.83 | < 0.001 |
| Chronic prostatitis in biopsy pathology | | | | |
| Yes | 283 | 8.38±6.94 | 7.06±5.62 | < 0.001 |
| No | 133 | 7.23±4.97 | 5.90±3.10 | 0.001 |
| PSA level (ng/mL) | | | | |
| < 4 | 46 | 2.48±1.09 | 2.29±1.16 | 0.116 |
| 4-9.9 | 293 | 6.48±1.63 | 5.91±2.01 | < 0.001 |
| ≥10 | 77 | 17.15±10.01 | 12.29±8.56 | < 0.001 |
| Prostate size (mL) | | | | |
| < 30 | 51 | 7.01±6.77 | 5.05±3.17 | 0.035 |
| 30-49.9 | 176 | 7.23±5.33 | 5.89±3.64 | < 0.001 |
| 50-69.9 | 107 | 7.38±4.54 | 6.69±3.66 | 0.033 |
| ≥70 | 82 | 11.15±8.97 | 9.45±8.01 | < 0.001 |

Values are presented as mean±standard deviation.
PSA, prostate-specific antigen.

DISCUSSION

Various physiologic and benign pathologic processes can lead to elevations of the serum PSA level. These factors include nonmalignant diseases of the prostate, such as benign prostatic hyperplasia, acute and subacute prostatitis, prostatic ischemia, and infarction of the prostate. Urinary retention and ejaculation can also lead to increased PSA levels in the absence of prostatic diseases. In addition, physical manipulation of the prostate, such as prostatic massages, cystoscopy, or in rare cases, digital rectal examination, can also increase serum PSA levels [3-8].

There have also been many studies of biological variations in serum PSA levels [11-13]. A more recent survey of 27 published studies suggested that a single measurement of the serum PSA level may not be sufficiently precise for screening and diagnosis of prostate cancer, because the mean biological variation of PSA is 20% in the range of 0.1 to 20 ng/mL for men over 50 years [14].

With regard to the daily variability in the serum PSA level, Mermall et al. [15] reported a circadian variation of serum PSA with a nadir value in the early morning and a peak value at midafternoon. By contrast, Tekin et al. [16] demonstrated a diurnal rhythm in PSA with a peak value at 08:00 and a gradual decline throughout the day until midnight. However, many other studies have reported that the variations in serum PSA values during a 24-hour period are random without any diurnal or circadian pattern [17-20]. Therefore, it is unlikely that there is an optimal time point during a 24-hour period at which to measure PSA, and blood samples for serum PSA values can be drawn from pa-

tients at any time of day [14,21].

There have also been a few reports about discrepancies between outpatient and inpatient serum PSA values in the same man. Stamey et al. [9] reported that serum PSA levels measured 24 hours after admission decreased by a mean of 18% with a maximum of 50% when compared with pre-admission levels. This may be due to the lack of activity associated with bed rest during hospitalization, and physical exertion owing to ambulatory status could cause an increase in serum PSA values. Leventhal et al. [10] confirmed the findings of Stamey et al. [9] by showing a significant difference between outpatient values and inpatient values measured after a minimum of 24 hours of bed rest. However, they found that the stressful exercise of cardiac stress testing during hospitalization had no effect on serum PSA values. Tekin et al. [16] also found that the serum PSA levels measured 72 hours after hospitalization significantly decreased by a median of 12% compared with the values obtained immediately before admission. Although the reasons for this decrease in the serum PSA level are uncertain, it is probable that the lack of activity compared with the preadmission ambulatory status could contribute to the decrease in serum PSA levels, because blood samples were obtained 24 to 72 hours after admission in the above 3 studies.

The effect of exercise on the serum PSA level is controversial. Whereas exercises such as bicycle riding increased the serum PSA levels in some reports [22,23], exercises such as bicycle riding or high-altitude trekking did not affect the serum PSA levels in others [24,25]. In the most recent study by Loprinzi and Kohli [26], participants were

16% more likely to have an elevated serum PSA level for every 1-hour increase in sedentary behavior, and were 18% less likely to have an elevated serum PSA level for every 1-hour increase in light physical activity. Therefore, those authors suggested that individuals who engage in more sedentary behavior and lower levels of light physical activity have higher serum PSA values.

In the current study, we obtained the blood samples for IPsPSA testing just after admission and found that the IPsPSA values were decreased compared with the pre-admission levels. Therefore, the effects of resting and sedentary behavior did not seem to influence the results. The diurnal variation in serum PSA values also might not have affected the results. The reasons for the decrease in serum PSA levels after hospitalization are still not certain. The decrease in IPsPSA levels compared with OPsPSA levels, although not significant, in patients aged 20–39 years and with PSA < 4 ng/mL might have been due to the small sample size of these subgroups compared with the other subgroups.

PSA variability may be related to analytical variation according to the methods of PSA measurement, sample handling, and laboratory processing [27]. Therefore, we excluded patients in whom OPsPSA was not measured in our hospital to eliminate the effects of analytical variation [28,29]. Serum PSA was measured by using two different immunoassay systems according to the period of PSA testing in our hospital. However, because our focus of analysis was the comparison of OPsPSA and IPsPSA in the same man with an interval between the two PSA measurements of within 1 month, and OPsPSA and IPsPSA in the same man were measured by using the same immunoassay system, there should be no analytical variation according to the laboratory processing. We also excluded patients with an interval of more than 1 month between OPsPSA and IPsPSA measurements to minimize the possible effect of biological variation in serum PSA levels. We also excluded patients who had a pathologic diagnosis of prostate cancer, because the serum PSA level might be influenced during the time interval between the OPsPSA and IPsPSA. In our previous report about short-term (median interval, 29 days; range, 7 to 90 days) PSA velocity before prostate biopsy in 670 patients with serum PSA levels of 2.5 to 20 ng/mL, median short-term PSA velocity (ng/mL/mo), which was defined as $(\text{IPsPSA} - \text{OPsPSA}) / \text{interval [days]} \times 30$, was significantly different between patients with benign histology and those with prostate cancer (-0.70 and -0.20 , respectively; $p=0.021$) [30].

This study had several limitations. This study was conducted in a single center. It was retrospective in nature and the size of the study population was small. The factor of recent ejaculation, which can affect the serum PSA level, was not analyzed in this study. Another limitation of our study is that the time of blood sampling was different for OPsPSA and IPsPSA. The blood sampling for the former was mostly done in the morning or early afternoon, whereas that for the latter was done in the late afternoon. As discussed ear-

lier, the influence of the timing of PSA measurement within a day is controversial. Moreover, the steps following the blood sampling, i.e., from the handling of samples until the analysis, were identical for both, excluding any possible influence from preanalytical differences.

Nevertheless, we believe that the IPsPSA levels were decreased compared with OPsPSA levels; thus, the hospitalization itself decreased the serum PSA levels. Therefore, serum PSA values should be measured on an outpatient basis for the serial monitoring of PSA. A larger prospective, multicenter study will be needed to confirm these results.

CONCLUSIONS

Hospitalization decreases serum PSA values compared with those measured on an outpatient basis in patients with benign prostatic diseases. Therefore, serum PSA values should be measured on an outpatient basis for the serial monitoring of PSA levels.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Jung KW, Park S, Kong HJ, Won YJ, Lee JY, Seo HG, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2009. *Cancer Res Treat* 2012;44:11-24.
2. Hong SY, Cho DS, Kim SI, Ahn HS, Kim SJ. Prostate-specific antigen nadir and time to prostate-specific antigen nadir following maximal androgen blockade independently predict prognosis in patients with metastatic prostate cancer. *Korean J Urol* 2012;53:607-13.
3. Greene KL, Albertsen PC, Babaian RJ, Carter HB, Gann PH, Han M, et al. Prostate specific antigen best practice statement: 2009 update. *J Urol* 2009;182:2232-41.
4. Herrmann M, Scharhag J, Sand-Hill M, Kindermann W, Herrmann W. Long-distance mountain biking does not disturb the measurement of total, free or complexed prostate-specific antigen in healthy men. *Clin Chem Lab Med* 2004;42:347-9.
5. Tchetgen MB, Oesterling JE. The effect of prostatitis, urinary retention, ejaculation, and ambulation on the serum prostate-specific antigen concentration. *Urol Clin North Am* 1997;24:283-91.
6. Lee AG, Choi YH, Cho SY, Cho IR. A prospective study of reducing unnecessary prostate biopsy in patients with high serum prostate-specific antigen with consideration of prostatic inflammation. *Korean J Urol* 2012;53:50-3.
7. Kratz A, Lewandrowski KB, Siegel AJ, Sluss PM, Chun KY, Flood JG, et al. Effect of marathon running on total and free serum prostate-specific antigen concentrations. *Arch Pathol Lab Med* 2003;127:345-8.
8. Ulman C, Buyukyazi G, Taneli F, Uyanik BS. Recreational and master athletic activity does not affect free and total prostate-specific antigen levels but lowers the free-to-total prostate-specific antigen ratio. *J Int Med Res* 2004;32:583-9.
9. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987;317:909-16.
10. Leventhal EK, Rozanski TA, Morey AF, Rholl V. The effects of exercise and activity on serum prostate specific antigen levels. *J*

- Urol 1993;150:893-4.
11. Komatsu K, Wehner N, Prestigiacomo AF, Chen Z, Stamey TA. Physiologic (intraindividual) variation of serum prostate-specific antigen in 814 men from a screening population. *Urology* 1996;47:343-6.
 12. Roehrborn CG, Pickens GJ, Carmody T 3rd. Variability of repeated serum prostate-specific antigen (PSA) measurements within less than 90 days in a well-defined patient population. *Urology* 1996;47:59-66.
 13. Nixon RG, Wener MH, Smith KM, Parson RE, Strobel SA, Brawer MK. Biological variation of prostate specific antigen levels in serum: an evaluation of day-to-day physiological fluctuations in a well-defined cohort of 24 patients. *J Urol* 1997;157:2183-90.
 14. Soletormos G, Semjonow A, Sibley PE, Lamerz R, Petersen PH, Albrecht W, et al. Biological variation of total prostate-specific antigen: a survey of published estimates and consequences for clinical practice. *Clin Chem* 2005;51:1342-51.
 15. Mermall H, Sothorn RB, Kanabrocki EL, Quadri SF, Bremner FW, Nemchausky BA, et al. Temporal (circadian) and functional relationship between prostate-specific antigen and testosterone in healthy men. *Urology* 1995;46:45-53.
 16. Tekin A, Atsu N, Ozen H. Daily variability of serum prostate-specific antigen in men over 50 years of age. *Int Urol Nephrol* 2001;33:641-4.
 17. Dejter SW Jr, Martin JS, McPherson RA, Lynch JH. Daily variability in human serum prostate-specific antigen and prostatic acid phosphatase: a comparative evaluation. *Urology* 1988;32:288-92.
 18. Mannini D, Maver P, Aiello E, Corrado G, Vecchi F, Bellanova B, et al. Spontaneous circadian fluctuations of prostate specific antigen and prostatic acid phosphatase serum activities in patients with prostatic cancer. *Urol Res* 1988;16:9-12.
 19. Akimoto S, Masai M, Shimazaki J. Relationship between diurnal rhythm of serum testosterone and two prostatic markers (PSA and PAP) in untreated prostate cancer. *Urology* 1994;43:337-41.
 20. Glenski WJ, Klee GG, Bergstralh EJ, Oesterling JE. Prostate-specific antigen: establishment of the reference range for the clinically normal prostate gland and the effect of digital rectal examination, ejaculation, and time on serum concentrations. *Prostate* 1992;21:99-110.
 21. Klein LT, Lowe FC. The effects of prostatic manipulation on prostate-specific antigen levels. *Urol Clin North Am* 1997;24:293-7.
 22. Rana A, Chisholm GD. He sold his bike for a low prostate specific antigen. *J Urol* 1994;151:700.
 23. Oremek GM, Seiffert UB. Physical activity releases prostate-specific antigen (PSA) from the prostate gland into blood and increases serum PSA concentrations. *Clin Chem* 1996;42:691-5.
 24. Crawford ED 3rd, Mackenzie SH, Safford HR, Capriola M. The effect of bicycle riding on serum prostate specific antigen levels. *J Urol* 1996;156:103-5.
 25. Verratti V, Di Giulio C, Di Francesco S, Berardinelli F, Pellicciotta M, Gidaro S, et al. Chronic hypoxia, physical exercise and PSA: correlation during high-altitude trekking (2004 K2 expedition). *Urol Int* 2007;78:305-7.
 26. Loprinzi PD, Kohli M. Effect of physical activity and sedentary behavior on serum prostate-specific antigen concentrations: results from the National Health and Nutrition Examination Survey (NHANES), 2003-2006. *Mayo Clin Proc* 2013;88:11-21.
 27. Shariat SF, Scardino PT, Lilja H. Screening for prostate cancer: an update. *Can J Urol* 2008;15:4363-74.
 28. Slev PR, La'ulu SL, Roberts WL. Intermethod differences in results for total PSA, free PSA, and percentage of free PSA. *Am J Clin Pathol* 2008;129:952-8.
 29. Brawer MK, Daum P, Petteway JC, Wener MH. Assay variability in serum prostate-specific antigen determination. *Prostate* 1995;27:1-6.
 30. Park JT, Kim SJ, Ahn HS, Kim YS, Choi JB, Kim SI. Short-term prostate-specific antigen velocity measurement before prostate biopsy. *Korean J Urol* 2009;50:553-9.