

Urinary PSA: a potential useful marker when serum PSA is between 2.5 ng/mL and 10 ng/mL

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Abstract

Introduction: Our objective was to evaluate the usefulness of urinary prostate specific antigen (PSA) in the differential diagnosis of benign prostatic hyperplasia (BPH) and prostate cancer.

Methods: We undertook a prospective study and obtained informed consent from 170 men. They provided blood samples to measure serum PSA and 50 mL of first-voided urine to measure urinary PSA. Seventy-seven men were diagnosed with BPH; 42 patients had newly diagnosed prostate cancer; and 51 were selected as age-matched control subjects. Data were analyzed using Wilcoxon signed rank tests, receiver operating characteristic (ROC) curves and logistic regression.

Results: Prostate volume was 35 cm³ and 45 cm³ ($p < 0.05$), serum PSA was 9.7 ng/mL and 4.5 ng/mL ($p < 0.001$) and PSA density was 0.28 and 0.11 ($p < 0.01$) for prostate cancer and BPH patients, respectively. Overall, urinary PSA was not significantly different, but PSA ratio (urinary:serum) was significantly different at 6.7 and 30.6 ($p < 0.001$) for prostate cancer and BPH patients, respectively. A subgroup with serum PSA between 2.5 ng/mL and 10.0 ng/mL was selected and urinary PSA was significant: 52.6 ng/mL ($n = 29$) and 123.2 ng/mL ($n = 35$) ($p < 0.05$) for prostate cancer and BPH patients, respectively. PSA ratios were also significant ($p = 0.007$). ROC curves identified a cutoff for urinary PSA at > 150 ng/mL, with a sensitivity of 92.5%. When comparing prostate cancer patients with age-matched control subjects, serum PSA, urinary PSA and PSA ratio were different ($p = 0.004$).

Conclusion: Our study supports urinary PSA as a useful marker in the differential diagnosis of prostate cancer and BPH, especially when serum PSA is between 2.5 ng/mL and 10 ng/mL. Low urinary PSA and PSA ratios point toward prostate cancer. A urinary PSA threshold of > 150 ng/mL may be used to decrease the number of prostatic biopsies.

CUAJ 2007;1(4):377-81

Introduction

Serum prostatic specific antigen (PSA) has proven to be a generally reliable indicator in the diagnosis and management of prostate cancer. It has revolutionized the management and follow-up of prostate cancer since its clinical introduction in the late 1980s. Serum PSA remains the best single test for the detection of early prostate cancer, and multiple variations have been studied to improve its sensitivity and speci-

ficity, first by associating it with the digital rectal examination and then by looking at age-adjusted PSA, PSA density, PSA velocity and percent free PSA. The upper limit of normal PSA (4.0 ng/mL) can also be lowered to 2.5 ng/mL or even lower because 20%–30% of tumours will be missed if the only method of detection is serum PSA with a cutoff of 4.0 ng/mL.¹

The pioneer work of Graves and colleagues,² who, in 1985, demonstrated the presence of PSA in urine, is still a matter of controversy when a role is tentatively ascribed to urinary PSA in cancer management.

Over the years, PSA has been measured on different samples: in urine voided before and after prostate massage,^{3,4} in first-voided urine,⁴⁻⁶ in single midstream sample of urine⁷⁻¹⁰ and in 24-hour urine specimens.¹¹⁻¹³ The fact that a urine specimen contains more PSA certainly appears to be an advantageous issue in terms of method of choice for PSA measurement.⁵

There is still no consensus among investigators about the possible role of urinary PSA in the diagnosis or follow-up of prostate cancer. Therefore, the aim of our study was to evaluate the usefulness of urinary PSA in the differential diagnosis between benign prostatic hyperplasia (BPH) and prostate cancer, especially when serum PSA is equivocal.

Patients and Methods

We undertook a prospective study after obtaining approval from the local research ethics board. Patients and urologists were blinded from the results; therefore, the usual clinical follow-up practice was not influenced by the actual study. None of the patients had

either urinary tract infection or symptoms of prostatitis. Patients were consecutively recruited during a scheduled clinic visit either before a transrectal ultrasound (TRUS) and biopsies (minimum of 8 core biopsies) for abnormal serum PSA or digital rectal exam (or both); or patients who had an established diagnosis of prostate cancer were recruited for participation when they presented for preadmission before a scheduled radical prostatectomy.

A total of 170 men gave an informed written consent and provided blood samples to measure serum PSA and bioavailable testosterone (normal range 2–14 nmol/L), which was analyzed in our laboratory. Bioavailable testosterone was measured to document the active androgen level of every patient and to avoid any bias. It was performed using the ammonium sulfate method as described by Tremblay and Dubé.¹⁴

At the same clinic visit, patients also provided a 50-mL sample of first-voided urine, any time during the day, but after at least 1 hour of continence, no sexual intercourse within 24 hours and before any rectal examination; these criteria were established from previous work within our laboratory (data not shown). We documented that urinary PSA reaches a constant level, for a particular individual, between 1 and 6 hours of continence, although urinary PSA remained at very high levels in the 24 hours following an ejaculation. We also documented that a prostatic massage had the same influence on urinary PSA.¹¹

Urine samples were stored at –20°C until assayed. Urinary PSA was expressed in ng/mL and an enzyme-linked immunosorbent assay (ELISA)

method was performed using a polyclonal antibody, “Poly PSA,” and a monoclonal antibody, “4D1,” that had been characterized in our andrology laboratory. Readings, by spectrophotometry, were done at 414 nm. This method has a sensitivity of 0.3 ng/mL and, intra- and inter-assay variations of 4%.

A group of 77 men were clinically diagnosed with BPH, 42 patients had a newly diagnosed prostate cancer and 51 men were selected as age-matched control subjects (no clinical symptoms of BPH). Patients with BPH, prostate cancer and age-matched control subjects had a median age of 64, 66 and 65 years, respectively. Patients diagnosed with prostate cancer subsequently underwent a radical prostatectomy. Serum PSA and urinary PSA were again obtained at their first postoperative follow-up visit. Wilcoxon signed rank tests, receiver operating characteristic (ROC) curves and a logistic regression adjusting for age, serum PSA and prostate volumes were used to analyze data.

Results

Overall, the patients within the 3 groups had comparable levels of bioavailable testosterone and therefore similar states of androgenicity (Table 1). As expected, prostate cancer patients had significantly higher serum PSA than patients with BPH and age-matched control subjects $p < 0.001$ (Table 1). Prostate volumes, measured by TRUS, were 35 cm³ and 45 cm³ ($p < 0.05$) and PSA density was 0.28 and 0.11 ($p < 0.01$) for prostate cancer and BPH patients, respectively. These 2 groups

Table 1: Results from sample analysis of all patients

Patient group	Bioavailable testosterone, nmol/L; median (and range); $p = 0.96$	Serum PSA, ng/mL; median (and range); $p < 0.001$	Urinary PSA, ng/mL; median (and range); $p = 0.10^*$	Urinary:serum PSA ratio; median (and range); $p < 0.001$
Prostate cancer ($n = 42$)	2.2 (1.2–3.0)	9.7 (6.9–13)	52.9 (17–113)†	6.7 (3–12)
Benign prostatic hyperplasia ($n = 77$)	2.6 (0.9–3.5)	4.5 (2.1–7.5)	75.7 (19–179)‡	30.6 (18–9)
Age-matched control subjects ($n = 51$)	2.5 (1.1–3.1)	2.1 (0.9–2.9)	105 (49–158)†‡	47 (30–75)

PSA = prostate specific antigen.

*Statistical comparison between the urinary PSA of prostate cancer patients and benign prostatic hyperplasia patients only.

†Urinary PSA for prostate cancer patients v. control subjects was statistically different ($p = 0.004$).

‡Urinary PSA for benign prostatic hyperplasia patients v. control subjects was statistically comparable ($p = 0.39$).

did not have a significant difference in urinary PSA levels when taken as a whole ($p = 0.10$), but PSA ratios were discriminative ($p < 0.001$) (Table 1). When we selected a subgroup of patients with serum PSA between 2.5 ng/mL and 10.0 ng/mL, with serum PSA being equivalent and adjusting for prostate volumes, median urinary PSA by itself was significant to discriminate prostate cancer from BPH ($p < 0.05$) (Table 2). PSA ratios remained significant in this subgroup ($p = 0.007$) (Table 2).

ROC curves and the area under the curve allowed us to identify a cutoff at 150 ng/mL for urinary PSA, with a sensitivity of 92.5% and a specificity of 36%, which was confirmed when comparing prostate cancer patients with age-matched control subjects. Urinary PSA levels > 150 ng/mL would be associated with BPH or a normal prostate in that age group and less with prostate cancer.

In a more specific comparison between prostate cancer and age-matched control subjects, serum PSA, urinary PSA and PSA ratio were significantly different ($p = 0.004$) (Table 1). When we analyzed the same parameters between BPH patients and the age-matched control subjects, serum PSA and PSA ratios were different ($p < 0.001$) but urinary PSA was comparable ($p = 0.39$) (Table 1).

The 42 patients with prostate cancer underwent radical prostatectomy and there was no difference in urinary PSA between lower (4–6) and higher (7–9) Gleason scores (median 49 ng/mL and 70 ng/mL, respectively; $p = 0.40$). The staging capacity was assessed and patients with stage T1 ($n = 5$) and T2 ($n = 21$) tumours had similar serum and urinary PSA as well as PSA ratios ($p > 0.20$); therefore, they were pooled together to be compared with stage T3 tumours. Pathological stage T3

tumours ($n = 16$) had a higher median urinary PSA compared with T1 and T2 tumours ($n = 26$), with 102.2 ng/mL and 35.2 ng/mL, respectively ($p < 0.04$). Conversely, PSA ratios (8.8 v. 3.8, respectively; $p = 0.14$) and serum PSA (11.0 v. 9.7, respectively; $p = 0.40$) were not significant to discriminate between these 2 groups.

We noted that urinary PSA of stage T3 tumours, in being significantly higher, was approaching levels measured for patients with BPH and serum PSA > 2.5 ng/mL, with median urinary PSA levels of 102.2 ng/mL and 123.2 ng/mL, respectively. Within that specific group of tumours, urinary PSA lost its discriminative power, but serum PSA remained significant ($p < 0.05$). PSA ratios were still effective and were calculated at 8.8 and 26.4 for stage T3 prostate cancer and BPH patients, respectively ($p = 0.008$). Within a group of patients with normally higher levels of urinary PSA but a low PSA ratio, or if the diagnosis of prostate cancer is confirmed with the same profile of urinary PSA and PSA ratio, one could suspect a higher stage of the tumour.

Patients diagnosed with prostate cancer all underwent a radical prostatectomy and, serum PSA and urinary PSA were again obtained at their first postoperative follow-up. Median serum PSA was 0.04 ng/mL (range 0–0.1 ng/mL) and urinary PSA was 0.5 ng/mL (range 0–1.1 ng/mL), confirming that minimal urinary PSA was secreted after exclusion of the prostatic gland.

Discussion

Theoretically, the measurement of urinary PSA should provide useful information about prostate physiology and pathology or both because

Table 2: Specific results for patients with prostate cancer or benign prostatic hyperplasia with serum PSA between 2.5 ng/mL and 10.0 ng/mL

Patient group	Prostate volume, cm ³ ; median (and range); $p = 0.04$	Serum PSA, ng/mL; median (and range); $p = 0.28$	Urinary PSA, ng/mL; median (and range); $p = 0.008^*$	Urinary:serum PSA ratio; median (and range); $p = 0.007$
Prostate cancer ($n = 29$)	36 (30–41)	7.2 (6.3–8.8)	52.6 (18–87)	8.8 (2.6–14)
Benign prostatic hyperplasia ($n = 35$)	47 (30–66)	6.2 (4.7–9.2)	123.2 (59–273)	26.4 (18–56)

PSA = prostate specific antigen.
 *When adjusting for prostate volume within a logistic regression, $p < 0.05$.

kallikreins are produced by epithelial cells lining the acini and prostatic ducts.¹⁵ In an abnormal state of the gland (chronic inflammatory process or neoplasia) characterized by stenosis, compression, neovascularization and disruption of the prostatic ducts, the polarity of the epithelial cells should be inverted to release the secreted kallikreins across the basement membrane thus reaching the bloodstream. Therefore, serum PSA should increase and urinary PSA consequently decrease. Following the initial publication by Graves and colleagues² in 1985, 2 years later, we reported data suggesting that urinary PSA and serum PSA was indeed altered in prostate cancer patients.¹¹ Twenty years later, the data of the present study indicate once more that patients with prostate cancer exhibit different urinary PSA and PSA ratios, compared with normal men or men with BPH. The theory seems to be supported by facts, and many investigators have obtained similar evidence.^{7,8,13,16-18}

Prostate cancer is the most frequent cancer in men and is the second highest cause of mortality by cancer for the male population. The diagnosis, however, requires an invasive investigation in many men. In fact, patients with a serum PSA between 2.5 ng/mL and 10 ng/mL will often undergo TRUS with prostate biopsies to rule out prostate cancer. Only 20%–30% of these men will have positive biopsies,^{1,19} meaning that the majority of men undergo these invasive investigations with little benefit. Serum PSA has been turned inside out to find new ways to differentiate prostate cancer from BPH before TRUS, and biopsies including, PSA density, age-specific PSA, percent free PSA and PSA velocity. The adjunct of new diagnostic tests to help differentiate these 2 pathologies might help us to reduce the number of negative TRUS biopsies.

Urinary PSA could be that kind of a tool, especially in the gray zone of serum PSA (2.5–10 ng/mL). We found an important difference between urinary PSA of prostate cancer and BPH patients. If used in conjunction with PSA ratio (urinary: serum), this improves the accuracy. A high urinary PSA (cutoff calculated at > 150 ng/mL) and high PSA ratio (> 15) point more toward BPH. A lower urinary PSA in the presence of prostate cancer is potentially explained by an altered drainage of prostatic secretions in the prostatic urethra. This leads to a diminution of urinary excretion of PSA, leading to an increase of PSA in the bloodstream,

causing an elevation of serum PSA in patients with prostate cancer. A disturbance in prostatic architecture with neovascularization would contribute to this mechanism.

In the presence of a higher stage (T3 tumour) of prostate cancer, urinary PSA overlapped with levels encountered in BPH, but these stage T3 prostate cancer patients had a median serum PSA of 11 ng/mL and low PSA ratios, both pointing to the presence of neoplasia. This observation has not been precisely described in previous studies and needs to be corroborated with larger numbers.

Conclusion

This study supports urinary PSA as a useful marker in the differential diagnosis of prostate cancer and BPH, especially when serum PSA is between 2.5 ng/mL and 10 ng/mL. Low urinary PSA and PSA ratios point toward prostate cancer. Urinary PSA could also help to stage a newly diagnosed prostate cancer, where higher stages presented higher measured levels. A urinary PSA threshold of > 150 ng/mL might be used to decrease the number of prostatic biopsies, but further studies are indeed required to corroborate our observations.

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This article has been peer reviewed.

Competing interests: None declared.

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CUAJ JAUC
Canadian Urological Association Journal / Journal de l'Association des urologues du Canada
Volume 1, Issue 1 / Volume 1, Numéro 1
March 2007 / Mars 2007

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ISSN 1911-4010

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