What are the possible reasons for urethral PSA varieties after radical prostatectomy?

**Objective:** To examine the possible reasons for great varieties in urethral prostate specific antigen (urPSA) levels, in patients after radical prostatectomy (RP). **Materials and methods:** In 46 patients with prostate cancer, PSA, urPSA, total testosterone, body-mass index (BMI) and the stage of androgenic alopecia (AGA) were determined. Forty-five patients underwent retropubic RP, while one underwent cystoprostatectomy with orthotopic bladder construction, due to bladder cancer. Results: Average patients age prior to surgery plus or minus standard deviation was 65.2 ± 5.8 years. Average urPSA was 20.9 ± 47.5 ng/ml (0.05 to 212 ng/ml, median 2.24 ng/ml). With urethral PSA cut-off of 2.0 ng/ml, two groups were formed: A (urPSA < 2.0 ng/ml) and B (urPSA = 2.0 ng/ml). Patients in the group A had significantly lower average AGA score, than the patients from the group B (2.4 ± 1.3 vs. 4.4 ± 2.2, p=0.0003). In addition, patients from the group A had significantly lower postoperative PSA (0.07 ± 0.08 ng/ml vs. 0.14 ± 0.06 ng/ml, p=0.0014). Conclusions: The patients with higher urPSA have higher AGA scores and higher postoperative PSA. This phenomenon is probably the consequence of higher local dihydrotestosterone activity in the scalp and PSA-secreting urethral glands.

Key words: Baldness, prostate specific antigen, radical prostatectomy, urethral glands, urethral PSA, urinary PSA.

**INTRODUCTION**

After successful radical prostatectomy, serum levels of prostate specific antigen (PSA) are usually very low. However, the acceptable PSA values among various patients may differ significantly, from 0.001 or less, to 0.2 ng/ml. Today, it is not quite clear where the source of PSA in the patients without relapse is. The possible sources of PSA are urethral epithelial cells and foci of cystitis cystica/glandularis but there is still no consensus about that. There is a great variety in urethral PSA production; these values may differ more than thousand times in the first urinary stream, from 0.1 to 100 ng/ml. As the urethral PSA production is under androgen control, these differences could be the consequence of different androgen activity in urethral epithelial cells, rather than the different penile or urethral size. Dihydrotestosterone (DHT) is the most important intracellular androgen and the main regulator of PSA expression in prostatic epithelial cells. As urethral PSA-secreting cells are morphologically identical to prostatic epithelial cells, DHT is most probably the main androgen that influences urethral PSA production. Increased intracellular DHT activity is responsible for the development of benign prostatic hyperplasia (BPH) and androgenic alopecia (AGA) in men; frequently, both conditions could be found in one patient.

**ANDROGENS AND BALDNESS**

The most important androgens in males are testosterone, which mediates masculinization in the adult, and DHT, which mediates prostatic growth, acne, facial beard, and male pattern baldness. Embryological development of both the hair follicle and the prostate depends on mesenchymal-epithelial interaction, which is influenced by the expression of 5-alpha reductase. Male pattern hair loss, or AGA, is the consequence of the progressive miniaturization of scalp hair. Observations in both eunuchs, who have low levels of testicular androgens, and males with low DHT due to genetic 5-alpha reductase deficiency, implicate DHT as a key androgen in the pathogenesis of AGA.

**ANDROGENS AND PSA SYNTHESIS**

The synthesis of PSA, the most important prostatic enzyme, is also DHT-dependent. After entering the epithelial cell, androgens react with 5-alpha reductase, which converts them into more potent hormone, DHT. The mo-
molecules of DHT bind to androgen receptor and enter the nucleus. In the nucleus, DHT-androgen receptor complex stimulates the transcription of various genes, for the synthesis of PSA, growth factors and other proteins. 

After the synthesis, PSA molecules are contained in prostatic secretory granules, which discharge their content out from the cell. Following that, PSA molecules leak through prostatic ducts to the prostatic urethra, where they collect, until the next micturition or ejaculation happens.

**URETHRAL PSA SECRETION**

Additional PSA molecules are secreted diffusely, along entire urethra, from so-called minor prostatic glands. All minor prostatic glands are made of prostatic glands, or of prostatic and mucinous epithelium. It seems that minor prostatic glands represent evolutionary remnant. Namely, early mammals, that appeared 65 million years ago, probably had primitive prostate consisted of disseminated prostatic glands in the urethra, so-called disseminated prostate. In the present time, small, microscopic disseminated prostates can be seen in whales and dolphins, and larger one in other mammals, like boar, ram and bull; the mammals on the higher evolutionary position, including primates, developed compact organ. In primates and humans, these glands probably provide diffuse presence of PSA in the urethra and, maybe, take place in the cleansing of the urethra after the ejaculation. All PSA molecules detected in the urine, were washed-out from the urethra during the micturition. Namely, 32.9 kDa heavy PSA molecule, cannot pass the glomerular membrane; it is proved that no PSA can be detected in the urine from ileal conduits, or nephrostomy catheters.

**MATERIALS AND METHODS**

*The patients*

This prospective-retrospective study enclosed 46 patients with prostate cancer without evidence of recurrent disease after surgery. Forty-five patients underwent radical retropubic prostatectomy, while one patient underwent cryostat prostatectomy with orthotopic bladder construction, due to bladder cancer. All patients underwent surgery from June 2000. to June 2008, in the Urological Clinic, Clinical Center of Serbia, Belgrade, by single urologist (T.P). The average age prior to surgery plus or minus standard deviation (SD) was 65.2±5.8 years (range 52 to 76 years), with the average follow-up of 41.7±24.9 months (12 to 110 months). Current average age ±SD was 67±6.6 years (range 53 to 82 years). There were no patients receiving additional therapy and all patients were free of urinary infection in the time of collecting urine specimen. The majority of patients collected multiple urPSA samples every three or six months; and average urPSA value was calculated.

**THE DETERMINATION OF PSA IN THE URINE**

All patients collected first 75ml (full urine-sample container) of the first morning urine at home and it was standard urine volume for the determination of PSA. All biochemical tests and measurement were done in the laboratory of Urological clinic, Clinical Centre of Serbia, Belgrade. For both serum and urinary PSA determination, Axsym PSA assay (Abbott Laboratories, Illinois, USA) was used. Total serum testosterone was determined postoperatively, using MEIA Abbott-Axsym assay. The methodology for processing PSA in the urine was described by Takayama in 1994. The urine was titrated with NaOH until the pH of 7.5 was reached. Urine samples were spun in the centrifuge at 2000 rpm for 10 minutes. Aliquots of 500 µl samples were frozen at -20°C and stored. Urine samples were thawed only ones prior to determination of PSA.

**HAMILTON- NORWOOD SCALE OF BALDNESS**

**TABLE 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Average AGA score</th>
<th>Postoperative PSA (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (urPSA &lt; 2 ng/ml)</td>
<td>21</td>
<td>2.4 ±1.3</td>
<td>0.07 ±0.08</td>
</tr>
<tr>
<td>B (urPSA ≥ 2 ng/ml)</td>
<td>25</td>
<td>4.4 ±2.2</td>
<td>0.14 ±0.06</td>
</tr>
<tr>
<td>p</td>
<td>-</td>
<td>0.0003</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

The assessment of the hair pattern and the grade of the androgenic alopecia (AGA) was done by competent urologist, using the illustration of the Hamilton-Norwood Scale of Baldness. (Figure 1) No attention was paid to the type of baldness, i.e. frontal or vertex baldness.
The calculation of Body Mass Index (BMI)

Body mass index was calculated postoperatively, as
next: body mass (kg) / body surface (m²). Normal values
of BMI for adult men aged 20 to 29 years are below
27.820.

THE STATISTICS

Statistical differences were calculated using Student’s t-

test for independent samples.

RESULTS

There were 36 patients with pT2N0 stage and 10 pa-
tients with pT3N0 stage. Average urethral PSA, plus or
minus standard deviation (SD), was 20.9±47.5 ng/ml
(range 0.05 to 212 ng/ml, median 2.24 ng/ml). Average
preoperative PSA was 8±4.3 ng/ml (range 1.2 to 24.3
ng/ml, median 7.2 ng/ml). The lowest PSA value be-
longed to the patient with bladder cancer. Average post-
operative PSA ± SD was 0.11±0.08 ng/ml (range 0.002 to
0.25 ng/ml, median 0.095 ng/ml). Average total testoster-
one ± SD was 15.2±6.6 nmol/L (range 6.1- 27.4 nmol/L).
Average prostate volume was 42.2±23.8 ml.

With urethral PSA cut-off of 2.0 ng/ml, two groups
were formed: A (urPSA < 2.0 ng/ml) and B (urPSA = 2.0
ng/ml). Patients in the group A had significantly lower
average AGA score, than the patients from the group B
(2.4±1.3 vs. 4.4±2.2, p=0.0003).

In addition, patients from the group A had significantly
lower postoperative PSA (0.07±0.08 ng/ml vs. 0.14±0.06
ng/ml, p=0.0014). (Table 1.).

However, there were no differences in current age,
BMI, and total testosterone level.

Likewise, there were no differences in preoperative PSA
and prostate volume.

There were no differences in definitive tumor stage, tu-

mor grade and Gleason score between the groups.

DISCUSSION

The development of the normal prostate, benign pro-
static hyperplasia (BPH) and prostate cancer (PCa) are
under genetic and hormonal influences. Likewise, male
pattern hair loss is the consequence of genetic predis posi-
tion and local androgenic metabolism35. It seems that bald
men have higher serum DHT, but similar serum testosterone,
compared to men with normal hair pattern. Ho-

wever, some authors found higher levels of free testoste-
one in men with vertex baldness, which can be consi-
dered as possible risk factor for PCa development. At last,
some authors found higher prevalence of AGA in the pa-
tients with larger prostates, as common consequence of
increased local DHT activity in the scalp and prostatic
epithelial cells. Finasteride, 5-alpha reductase (5-ARI) ty-
pe II inhibitor and dutasteride, dual 5-ARI, markedly
decrease serum and intraprostatic DHT concentrations,
as well as DHT concentration in the hair follicle22-26. As
both genetic and hormonal factors play an important role
in the development of all human organs, baldness could
serve as a good surrogate marker for genetic and local
DHT influences.

Despite the fact that PSA concentration is higher in the
urine than in the blood, uPSA determination has never
been routinely used in the clinical practice. Nevertheless,
the fact that urinary PSA levels strongly depend on andro-
gen level and follow the changes in androgen concentra-
tions is well known. In the first scientific issues, high con-
centrations of PSA were found in the urine of patients
with BPH, and low concentrations in the urine of patients
after RP. However, while some authors found significant
differences in serum-to-urinary PSA ratio in patients with
BPH and PCa, the others did not27-30. Later studies pro-
ved that uPSA in patients that underwent RP, originates
from periurethral glands. The synthesis and production of
PSA was detected even in female urethral glands, after
testosterone administration in female-to-male transsex-
uals31,32.

Increased local DHT production is probably the co-

mmon cause of increased PSA synthesis, prostatic epi-
thelial cells growth and AGA. However, urethral minor
prostatic glands represent better model for the evaluation
of DHT influence on PSA production, than the whole
prostate gland. Namely, urethral PSA production can be
clearly measured in the urine, while many factors com-
plicate the assessment of PSA production in the prostate
gland. The examination of isolated urethral PSA pro-
duction is possible only in the absence of the prostate, i.e. af-
ter RP.
In this issue, men after radical prostatectomy, without evidence for recurrent disease, had urethral PSA values from 0.05 to 212 ng/ml, median 2.24 ng/ml. (The patient with highest urPSA had constantly high urPSA levels from January 2007 and low PSA, measuring 0.1 ng/ml; his BMI was 24.1 and his body hair distribution and penile length usual).

The patients with urPSA = 2.0 ng/ml had higher AGA score and higher postoperative PSA than the patients with urPSA < 2.0 ng/ml and that were the only differences between these two groups. There were no difference in average age, BMI, preoperative prostate vo-lume, tumor grade and stage between the groups. It seems that the difference emerged due to higher local DHT ac-tivity in target tissues, i.e. in the PSA-secreting urethral glands and the scalp. Although it was expected that the patients with higher urPSA had larger prostates before surgery, it was not proved.

The intriguing fact is that patients with higher urPSA had higher postoperative PSA, but there were no correlation between urPSA and postoperative PSA level. However, there is a possibility that urethral PSA production takes part in the total serum PSA concentration after radical prostatectomy. Indeed, in the group with urPSA = 2.0 ng/ml, there were three patients with urPSA over 100 ng/ml, which is comparable with prostatic PSA production. In the previous report, in the group of patients with BPH, the authors found urethral PSA levels ranged from 28.7 to 445 ng/ml, median 206.8 ng/ml [33]. However, this hypothesis has to be proved in further investigations.

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**REZIME**

**KOJI SU MOGUĆI RAZLOZI VELIKIH VARIJACIJA PSA POSLE RADIKALNE PROSTATEKTOMIJE**

**Cilj rada:** Ispitati koji su mogući uzroci velikih varijacija vrednosti uretralnog prostata specifičnog antitena (urPSA), između različitih bolesnika kod kojih je učinjena radikalna retropubična prostatektomija (RRP).

**Materijal i metode:** Kod 46 bolesnika sa lokalizovanim karcinomom prostata određivani su PSA, urPSA, ukupni kal prostatectomy. Indeed, in the group with urPSA = 2.0 ng/ml, there were three patients with urPSA over 100 ng/ml, which is comparable with prostatic PSA production. In the previous report, in the group of patients with BPH, the authors found urethral PSA levels ranged from 28.7 to 445 ng/ml, median 206.8 ng/ml [33]. However, this hypothesis has to be proved in further investigations.

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**Zaključak:** Posle RRP, bolesnici sa višim urPSA imaju viši stepen AGA i viši postoperativni PSA. Ovaj fenomen je verovatno posledica veće lokalne aktivnosti dihidrotestosterona u koži glave i u uretralnim žlezdamima koje proizvode PSA.

**REFERENCE**


17. Kabalin JN, Hornberger JC: Prostate specific antigen is not excreted by human kidney or eliminated by routine hemodialysis. Urology, 1991; 37:308-310


