



Benign prostatic hyperplasia and prostate-specific antigen

Benigna hiperplazija prostate i prostata specifični antigen

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Key words:
prostatic hyperplasia; prostate-specific antigen;
prognosis.

Ključne reči:
prostata, hiperplazija; prostata, specifični antigen;
prognoza.

Androgens and prostate function

Testosterone (T) and 5 α -dihydrotestosterone (DHT) play a crucial role in the fetal prostate development. These androgens stimulate mesenchyme, while mesenchyme induces the proliferation of the epithelial buds from the urogenital sinus. This process, called “mesenchyme-epithelial interaction”, starts in the 10th gestational week and continues in the adult age^{1,2}. Testosterone induces the development of the seminal vesicles and Wolffian ducts, while DHT induces the development of the prostate, penis and scrotum.

Prostatic tissue is composed of stroma and epithelium. Prostatic stroma is composed of stromal cells (fibroblasts, endothelial capillary cells, lymph vessels and smooth muscle cells), neuroendocrine (NE) cells, neural cell axons, intercellular liquid and collagen fibers³. Prostatic epithelium is composed of secretory, basal, intermediary and NE cells. Secretory cells synthesize and secrete various proteins, like prostate specific antigen (PSA), prostatic acid phosphatase (PAP), androgen receptor (AR) and make the greatest part of the prostatic epithelium. It is believed that NE cells induce growth, differentiation, and secretory functions of the prostatic epithelium⁴.

Numerous factors regulate prostatic growth: endocrine, neuroendocrine, paracrine, or growth factors (GF), autocrine and intracrine factors. However, the action of the endocrine factors is the best known. Testosterone is the most important serum androgen in the male, with the average serum concentration of 611 ± 186 ng/dL, while the average DHT serum concentration is 56 ± 20 ng/dL. However, the average concentration of active, free T is only 12.1 ± 3.7 ng/dL, while the rest is bound to the globulins and albumins. The major androgen in the prostatic tissue is DHT, with the average tis-

sue concentration of 2.4–5.1 ng/g. The average tissue concentration of T is 3–5 times lower and measures 0.9 ng/g⁵⁻⁷.

Only free T molecules can enter the prostatic cell, by diffusion. In the cytosol, one part of T molecules transforms into DHT. Both T and DHT bind to AR and form androgen-AR complexes. Subsequently, those complexes make pairs, entering the nucleus and bind to androgen-responsive elements (ARE) on DNA. After the information was transcribed from DNA to mRNA, mRNA leaves the nucleus and comes on ribosomes, where the information is translated into protein. Enzyme 5- α reductase (5 α R) performs the conversion of T to DHT. There are two isoforms of 5 α R: type 5 α R-2 is dominant in the prostatic stroma and accessory genital tissues. Type 5 α R-1 is present in the skin and prostate epithelium.

Benign prostate hyperplasia

Benign prostate hyperplasia (BPH) denotes progressive prostatic enlargement, associated with the symptoms of impaired emptying of the urinary bladder and followed with gradual progression of the symptoms and complications. The most common BPH-related complications are chronic urinary infection, urinary bladder stones, chronic and acute urinary retention. The prevalence of BPH is very high: BPH is the fourth most common disease, after coronary disease, hypertension and diabetes. In 2010, 210 million of men, or 6% of general population, suffered from BPH^{8,9}. According to Pan European Expert Project “Triumph”, the prevalence rate of urinary symptoms suggestive for BPH is the lowest among males 45–49 years old (2.7%) and increases with age, until a maximum at 80 years (24%)¹⁰. On the other hand, the prevalence of histological BPH found on autopsy material is

much higher: it is 10% for men in IV decade, 20% for men in V decade, 50–60% in men in VII decade and 80–90% in men in VIII and IX decade ¹¹.

Etiology of benign prostatic hyperplasia

The most common factors that induce the development of BPH are steroid hormones, growth factors, interactions between stroma and epithelium, and the regulation of apoptosis (Figure 1). The gradual decrease of T concentration is characteristic for an aging man; however, DHT concentration increases in prostatic tissue, or remains unchanged. The role of estrogens and estrogen receptors (ER) in the etiology of BPH is very possible. It is proved that dog prostate contains large amounts of ER and that estrogen administration induces stromal growth in dogs. In humans, epithelial proliferation is stimulated by fibroblast growth factors (FGF) and inhibited by transforming growth factors (TGF). The concentration of TGF- β is decreased in BPH ¹². In brief, the development of BPH requires androgenic influence in young age and long-term androgen stimulation in adult age. In old age, characteristic events are the decrease of T concentration and the increase of DHT and estrogen concentration, increased FGF activity, decreased TGF- β activity and the decreased apoptosis.

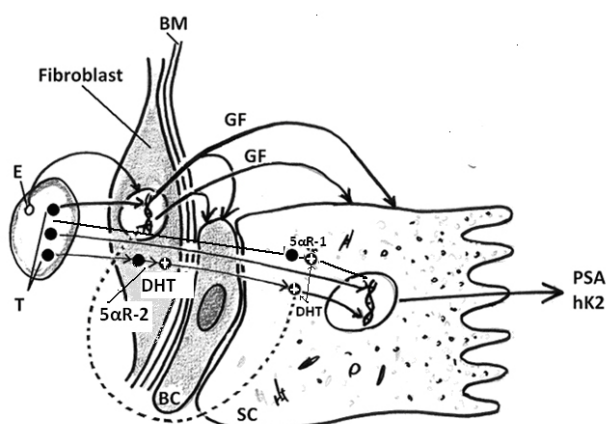


Fig. 1 – Stromal-epithelial interaction (Autor T. Pejčić)

E – estrogen; T – testosterone; DHT – dihydrotestosterone; 5 α R-1 – 5-alpha reductase type-1; 5 α R-2 – 5-alpha reductase type-2; BM – basement membrane; GF – growth factor; BC – basal cell; SC – secretory cell; PSA – prostate-specific antigen; hK2 – human kallikrein 2.

Benign prostatic hyperplasia is common among members of Western civilization; however, there is an increasing incidence of BPH in Asian countries, with traditionally low prevalence of BPH ¹³. It is believed that the increase in incidence is associated with the lifestyle of the modern man. In fact, today's man is fed differently than his ancestors, live longer and retains sexual activity long after the generative period. Humans have drastically changed diet about 15,000 years ago, when domesticated animals and, of obligate herbivores, became carnivorous ¹⁴. Excessive intake of meat, fried and baked foods and obesity, lead to hormonal disturbances and oxidative DNA damage ¹⁵. In developed coun-

tries, the average human life span is today over 80 years, while the length of human life in the Neolithic period was only 20 years ^{16, 17}. In addition, the man retains sexual activity for a long period: 20–35% of men aged 60–69 years have one intercourse *per week* ¹⁸. Unlike most of primates, man's sexual activity does not have seasonal variations. Therefore, long-term hormonal stimulation of the prostate, oxidative stress and increased incidence of genetic changes associated with aging are all important combined etiological factors for the development of BPH.

Pathology and pathophysiology of benign prostatic hyperplasia

Prostatic hyperplasia increases urethral resistance, which leads to a compensatory increase in detrusor pressure and the reduction in bladder capacity. It is believed that the capsule of the prostate plays a very important role in the development of lower urinary tract symptoms (LUTS), because it transmits the pressure of the hyperplastic tissue on the urethra.

The important characteristic of BPH is the increase of the total number of cells, not only an increase in cell size. McNeal has shown that early periurethral nodules have a stromal structure, while the early nodules in the transition zone (TZ) represent the proliferation of the glandular tissue. Glandular nodules rise from the newly formed small ducts, arising as buds on existing ducts; these ducts grow and branch out, creating an entirely new ductal system within the nodule. During the first 20 years, the development of BPH is characterized by an increased number of slowly growing nodules. Thereafter, in the second stage, major nodules show significant growth ¹⁸.

Clinical characteristics of benign prostatic hyperplasia

Common characteristics of BPH are progressive enlargement of the prostate, voiding symptoms and increased PSA. Total prostate volume (TPV) increases from 25 mL in men aged 30–35 years, to 45 mL in men over 70, while the transition zone (TZ) volume increases from 15 mL to 25 mL. Transrectal ultrasound (TRUS) provides the most accurate measurement of TPV. The Olmsted study revealed that TPV grows 0.4 mL per year in men aged 40–59, and 1.2 mL *per year* in men aged 60–79. The overall TPV growth was 0.6 mL, or 1.9% *per year*.

Lower urinary tract symptoms are typical for BPH ²⁰; however, LUTS is also common in men with the stenosis of the urethra, or the weakness of the detrusor muscle. That was the reason for the introduction of the new terms, like "bladder outlet obstruction" (BOO), "benign prostatic obstruction" (BPO) and "benign prostatic enlargement" (BPE). In the Serbian literature, symptoms of urinating are commonly classified as "irritative" (urgency, pollakiuria, nocturia) and "obstructive" (waiting for the beginning of urination, straining to urinate, interruption of the urinary stream). The severity of the symptoms can be expressed using the International Prostate Symptom Score (IPSS). The symptom score ranges

from 0–35. However, the obstruction can be assessed objectively by the measurement of the urinary flow, or Uroflow. It is accepted that the maximum urine flow, $Q_{\max} < 10$ mL/sec, carries a high probability for the presence of the obstruction, while $Q_{\max} > 15$ mL/sec carries a low probability. Some authors tried to express urine flow through the single number, Q_i . Index Q_i is the result of multiplying Q_{\max} and average flow, Q_{ave} : $Q_i = Q_{\max} \times Q_{\text{ave}}$. Pejčić et al.²⁰ found that 71% of men with IPSS > 7 had $Q_i < 100$, while 75% healthy men with IPSS < 7 had $Q_i > 100$.

Prostate – specific antigen

The main secretory proteins of the prostate gland are prostate-specific antigen (PSA), human glandular kalikrein (hK2), prostatic acid phosphatase (PAP) and prostate-specific protein (PSP-94). Molecular weight of PSA is 34 kDa; PSA molecule consists of one chain with 240 amino acids and four carbohydrate lateral chains (Figure 2).

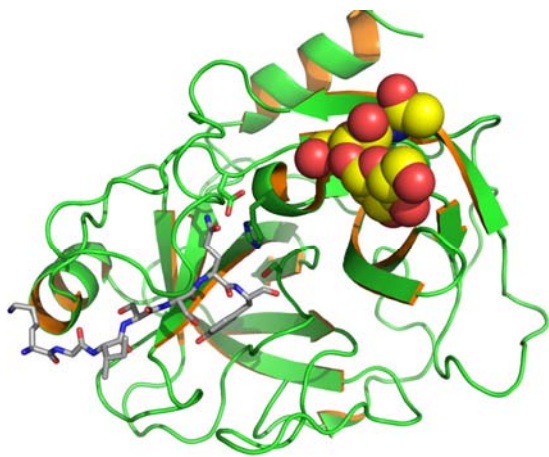


Fig. 2 – Human prostate-specific antigen (PSA/KLK3) with bound substrate from complex with antibody²¹.

Prostate-specific antigen was isolated in seminal plasma in 1966; for a long time, PSA has been used in forensic evidence of rape²². It has been estimated that the PSA concentration in seminal plasma was very high (1.5 mg/mL) and lower in urine (250 ng/mL). However, Wang et al.²³ were the first to predict the possible use of PSA determination in the blood in the diagnosis of the prostate diseases. The average PSA concentration in the prostatic tissue ranges from 10,000 ng/mg of tissue to 76,000 ng/mg of tissue^{24, 25}. In other words, prostate gland weighing 20 mL contains 0.2–1.5 mg PSA. The expression of PSA is high in benign epithelial cells, low in malignant cells and progressively decreases with the degree of anaplasia^{26–31}.

Synthesis and secretion of prostate-specific antigen

The intensity of PSA synthesis largely depends on the concentration of DHT in the prostatic tissue³². DHT molecules bind to AR and form DHT-AR complexes. Those complexes enter the nucleus and bind to ARE on the DNA. The

following is a transcription to mRNA; after that, mRNA leaves the nucleus and goes to the ribosomes, where the translation and PSA synthesis take place^{33, 34}. Alternative PSA synthesis pathway was demonstrated in the tissue culture. This pathway goes *via* the membrane steroid receptor; it is considerably faster than the genomic process and lasts 1–30 minutes³⁵.

The first product of the synthesis is the preproPSA molecule, with a leading sequence of 17 amino acids. PreproPSA molecules are placed in a number of prostate secretory granules (PSGs), which migrate towards the apical part of the cell. During the following biochemical process, leading sequence of 17 amino acids is separated from the preproPSA molecule. This product is now referred to as proPSA, and it is ejected as an inactive proenzyme from a cell *ie* secreted into the lumen of the acinus. In the lumen of the acini, hK2 separates another seven amino acids from the proPSA molecule, which results in the creation of active enzyme PSA. The last reaction which happens in the acini is very important: acinar enzymes change the conformational structure of the PSA molecule, after which it becomes inactive as an enzyme. In normal acini, 25–30% of the PSA molecules are inactivated and thereafter diffuse into the systemic circulation. The remaining PSA molecules enter blood as active enzymes, where they rapidly form complexes with heavy plasma proteins. One fraction of PSA molecules does not enter blood, but leaks down the acini and ducts, as a part of prostatic secretion. Secretion is moving towards prostatic urethra due to the difference in hydrostatic pressure and stromal smooth muscle tone.

The prostatic urethra is closed most of the time, due to the muscle tone of the proximal and distal urinary sphincter. During this time, prostatic secretions are constantly entering the urethra, through a number of holes around the verumontanum. Secretion accumulates in the urethra until the first voiding, when the flow of urine ejects it out of the body. All PSA molecules detected in the urine were made in the prostate and urethra: PSA molecule is too large to pass the glomerular membrane of the kidney³⁶. Therefore, it should be named "secreted PSA", rather than "urinary PSA". PSA molecules detected in urine are all in the free form, with the weight of 32.9 kDa and are chemically and structurally identical with the PSA molecules of seminal plasma³⁷. The normal healthy prostate gland secretes 0.01–0.02 mg PSA *per* day, while hyperplastic prostate secretes ten times larger amounts of PSA. During sexual inactivity, prostatic secretion rich with PSA molecules leak slowly to the prostatic urethra, so around 10–100 ng PSA gather in the urethra between two urinations. However, during the sexual act, parasympathetic nerves stimulate the increased PSA discharge from the cell; meanwhile, stromal muscles squeeze the secretion from the acini and inject it into the urethra in a large quantity. Before ejaculation, 5–6 mg of PSA is collected in the prostatic urethra. The PSA concentration in seminal plasma is 0.3–3 mg/mL^{38–40}. Only in the ejaculated semen, PSA molecules perform their function: they split the proteins of the seminal clot and thus allow active sperm motility⁴¹.

Prostate-specific antigen in serum

Under normal conditions, 25–30% of the inactive PSA molecules and 70–75% of active PSA molecules enter blood stream. As soon as the active PSA molecules enter blood, they are immediately bound by protease inhibitors, such as antichymotrypsin (ACT) and alpha 2-macroglobulin (alpha-2M). This process is fast and efficient because the molar concentration of the inhibitors exceeds molar PSA concentration over 100,000 times. PSA-ACT complex is the most common PSA form in serum, and is formed in the 1 : 1 molar ratio, in the irreversible reaction. These molecules can be detected in blood tests and they are named "complexed PSA". On the other hand, inactive PSA molecules can be detected as the fraction of free molecules and they are named "free PSA". In the presence of prostatic acinar lesion, smaller fraction of active PSA molecules completes the transformation to an inactive PSA; that is the explanation why free PSA fraction is lower in patients with prostate cancer (PCa).

It is not yet exactly known how PSA molecules enter blood. However, it is known that PSA molecules have to cross the so-called "prostatic blood-barrier", consisting of prostatic basal cells, basement membrane of the duct, the extracellular space, the capillary basement membrane and the layer of capillary endothelial cells. All processes which lead to damage of the prostatic blood-barrier enable massive PSA transfer in blood^{42, 43}.

Determination of PSA in serum in the diagnosis of BPH

Clinical application and research related to PSA over the last 25 years have been so extensive, that this period of urology is called the "PSA era". What is even more important, the occurrence of PSA strongly influenced the tremendous changes in the diagnostics and treatment of prostate cancer (PCa) and the development of new strategies and technologies for the treatment of this disease. However, the phenomenon of elevated PSA in BPH patients has always been regarded as the "artifact", which complicates the diagnosis of localized PCa.

It has long been thought that normal PSA level is below 4.0 ng/mL. However, subsequent studies have shown two confusing facts. First, it became clear that a significant number of patients with localized PCa had PSA < 4.0 ng/mL; soon, the new PSA cut-off value of 2.5 ng/mL was established^{44, 45}. Second, it has been proven that 70–80% of people without PCA after biopsy, had PSA within the "gray zone" i.e., 4.0–10.0 ng/mL. It became clear that the PSA level in each subject depends on many factors. In the first place, the synthesis of PSA depends on the concentration of DHT, as well as the presence of BPH. Then, the level of PSA depends on the hormonal status, obesity, body weight, total blood volume and so on. In patients with localized PCa, the size and location of the tumor also influence the PSA level. Finally, serum PSA level depends on the concentration of PSA in prostatic tissue surrounding the growing tumor⁴⁶.

The so-called "PSA derivatives" were introduced in order to distinguish the patients with BPH and PCA, with the

PSA in gray zone. PSA density (PSAD) was introduced with the aim to reduce the impact of prostate size on the interpretation of the PSA. For the threshold is taken $PSAD = 0.1$, i.e., patients with $PSAD > 0.1$ are more likely to have PCa⁴⁷. Similarly, subjects with PSA velocity (PSAV) > 0.8 ng/mL per year, have greater risk for the presence of PCa. Those with $PSAV \leq 0.8$ ng/mL per year are more likely to have BPH. A derivative called "PSA doubling time" (PSADt) expresses the increase of PSA in time (t) more precisely; it is calculated using the formula: $PSADt = \log 2t / \log \text{final PSA} - \log \text{initial PSA}$. Prostate cancer has shorter PSADt than BPH; in addition, the more aggressive the tumor is, PSADt is shorter^{48, 49}. Free/total PSA ratio (f/t PSA) is frequently used to distinguish the persons with BPH and PCa having PSA in the gray zone and normal digital rectal examination (DRE). Normal values of f/t PSA are 0.18 to 0.22⁵⁰; however, the patients with f/t PSA < 0.1 have 56% chance to have PCa⁵¹.

Today, it becomes quite clear that BPH is the main reason for the PSA values from 4.0–10 ng/mL, or 2.5–10 ng/mL. The American Urological Association (AUA) states that a very high risk for the presence of PCa, about 90%, is present in PSA > 20 ng/mL. It is not difficult to conclude that the increase in PSA, caused by the presence of BPH, was the main reason for the unnecessary diagnosis of a large number of clinically insignificant PCa. This is one of the reasons why the AUA reduced the range of PSA screening for men aged 55 to 69 years in 2013.

On the other hand, in the field of BPH, the situation is far less complicated and PSA is a precise parameter of disease progression. Several large multicenter studies have defined the precise parameters for monitoring the growth and progression of BPH. The most well-known studies are: Proscar Long-Term Efficacy and Safety Study (PLESS), Medical Therapy of Prostatic Symptoms (MTOPS), "Olmsted County Study of Urinary Symptoms and Health Status Among Men" and The Combination of Avodart and Tamsulosin (CombAT).

MTOPS study included 3,047 patients, who were followed for 4.5 years. Factors that indicated the progression of BPH were $TPV \geq 31$ mL, $PSA \geq 1.6$ ng/mL, $Q_{max} < 10.6$ mL/s, residual urine, $RU \geq 39$ mL and the age ≥ 62 years⁵². In patients who were taking finasteride, the average reduction in TPV for 4.5 years was 19%. However, men with $TPV > 40$ mL had an average reduction in TPV by 25%^{53, 54}. CombAT study included 4,844 men aged over 50 years with a clinical diagnosis of BPH, $IPSS > 12$, $TPV > 30$ mL, PSA in the range of 1.5–10 ng/mL and at least two urinations with Q_{max} of 5–15 mL/s⁵⁵.

Average TPV was 43 mL, and the mean PSA, 3.6 ng/mL. It was concluded that a combination therapy was better for patients with $TPV < 43$ mL and $PSA < 3.6$ ng/mL, and that in the patients with higher values, dutasteride was as effective as the combined therapy. After 24 months, the decrease of TPV was 30.5% (combination therapy), or 28.6% (dutasteride). These studies conclude that the enlarged prostate and elevated PSA are good predictors of complications such as acute urinary retention and need for surgery, while the severity of symptoms and lower flow often behave paradoxically^{56–58}.

Determination of PSA in the urine in the diagnosis of BPH

Determination of PSA concentration in urine (uPSA) has never been used in the diagnosis of BPH and monitoring of BPH progression. It is interesting that even in 1987, Tremblay et al.⁵⁹ found that the average uPSA concentration was 216 ng/mL and that people with BPH had higher uPSA values than young men. However, over the following years, researches have focused mainly on the ability to distinguish BPH and PCa and to detect early relapse after radical prostatectomy (RP). From 1994 to 2000, few works on this topic concluded that uPSA was higher in BPH than in PCa, but that it cannot help in differentiating those two diseases⁶⁰⁻⁶³. The hope that uPSA will become a marker of the early recurrence after RP, was closed when Iwakiri et al.⁶⁴ demonstrated that PSA was normally present in urine in all patients after RP and that it originated from the urethral glands⁶⁴. In some studies, it has been found that men with alopecia had higher values of urethral PSA after RP⁶⁵.

All researchers agree that uPSA is highly androgen-dependent marker for monitoring of the hormonal treatment, in both men and women^{66, 67}. Also, uPSA can be used as an early noninvasive marker of the appearance of puberty in boys^{68, 69}. In most primates, the seasonal uPSA increase indicates the beginning of the breeding season⁷⁰. Except the determination in fresh urine, uPSA can be determined in the dried urine, on filter paper, where it remains stable over a long period of time⁷¹. However, most researchers agree that the methodology of PSA determination in urine is still inconsistent⁷².

In recent years, several papers that trigger the clinical use of uPSA were published. In a group of patients with PSA of 2.5–10.0 ng/mL, Bolduc et al.⁷³ found a significant difference in mean uPSA in BPH (123.2 ng/mL) and PCa (52.6 ng/mL). With the uPSA threshold > 150 ng/mL, the sensitivity of the test was 92.5%. The authors believe that subjects with PSA of 2.5–10.0 ng/mL and uPSA > 150 ng/mL, could be exempted from prostate biopsy, in the absence of suspicious lesions on DRE and TRUS. In some studies, it has been found that larger tumors had lower uPSA than smaller tumors, probably due to the obstruction of the drainage of secretions⁷⁴⁻⁷⁶.

However, only one paper described the methodology of uPSA usage as a prognostic marker of BPH⁷⁷. In a group of 265 patients without PCa, uPSA, PSA, TPV and patients' age were determined. According to MTOPS criteria, TPV ≥ 31 mL, PSA ≥ 1.6 ng/mL and age ≥ 62 years were used as cutoff values of BPH progression. Persons with TPV < 31

mL had significantly lower uPSA, than patients with TPV ≥ 31 mL (119.3 ± 124.5 and 255.5 ± 204.9 ng/mL, respectively; $p < 0.0001$). In addition, persons in the so-called "non-progressive BPH" group (TPV < 31 mL, PSA < 1.6 ng/mL, age < 62 yrs) had significantly lower uPSA than patients from the "progressive BPH" group (86.8 ± 82.4 ng/mL and 274.9 ± 208.3 ng/mL, respectively; $p < 0.0001$). Urinary PSA correlated significantly with TPV ($r = 0.32$, $p < 0.0001$).

The urinary PSA cutoff level of 150 ng/mL discriminated the patients with non-progressive BPH and progressive BPH with specificity of 0.83 and sensitivity of 0.67. In that issue, Pejčić et al.⁷⁷ conclude that uPSA reflects prostatic hormonal activity and correlates with TPV, PSA and age. Therefore, uPSA level ≥ 150 ng/mL can be used as an additional predictive parameter of BPH progression.

Conclusion

Testosterone and 5 α -dihydrotestosterone play a crucial role in the prostate fetal development, growth and function. Testosterone is the most important serum androgen in the male, but the major androgen in the prostatic tissue is 5 α -dehydrotestosterone.

Benign prostatic hyperplasia is the fourth most common disease and affects 6% of general population. Biochemical characteristics of benign prostatic hyperplasia are decreased testosterone, increased 5 α -dehydrotestosterone and estrogen concentration, increased fibroblast growth factor and decreased transforming growth factor-beta activity.

Prostate-specific antigen is the main secretory product of the prostate gland; its synthesis largely depends on the 5 α -dehydrotestosterone concentration in the prostatic tissue. Normal healthy prostate gland secretes 0.01–0.02 mg prostate-specific antigen per day, while hyperplastic prostate secretes ten times larger amounts of prostate-specific antigen. Secreted prostate-specific antigen is washed out from the urethra during voiding and can be detected in the urine.

However, the phenomenon of elevated prostate-specific antigen in benign prostatic hyperplasia patients has always been regarded as the "artifact", which complicates the diagnosis of localized prostate cancer. Nevertheless, recent studies precisely established that serum prostate-specific antigen ≥ 1.6 ng/mL is suggestive for benign prostatic hyperplasia progression in men with prostate volume ≥ 31 mL and age ≥ 62 years. In addition, urinary prostate-specific antigen concentration is significantly higher in subjects with benign prostatic hyperplasia; urinary prostatic antigen level ≥ 150 ng/mL can be used as additional predictive parameter of benign prostatic hyperplasia progression.

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Received on November 30, 2013.

Revised on March 4, 2014.

Accepted on March 6, 2014.

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