

Growth Factors in Blood Serum of the Patients with Benign Prostatic Hyperplasia

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ABSTRACT. The aim of the present research is to define concentration of growth factors in the blood serum of the patients with benign prostatic hyperplasia (BPH). It has been established by means of high-sensitive immunoenzyme analysis that the patients with BPH aged 57-81 have higher basic fibroblast growth factor (bFGF) concentration compared with control group (healthy men). In most cases bFGF is found among 1.6 ± 10.5 to 44.0 ± 10.8 pg/ml, whereas β -1 transforming factor concentration is low and varies from 19.1 ± 2.2 to 3.5 ± 1.2 pg/ml. © 2007 Bull. Georg. Natl. Acad. Sci.

Key words: basic fibroblast growth factor, β -1 transforming growth factor and benign prostatic hyperplasia.

I. Introduction

Benign prostatic hyperplasia is one of the vital ones in medical and demographic, social and economic aspects [1] and the problem of its pathogenesis is of topical importance in urology. Prostate is an androgen-dependent organ though androgens have a mediated mitogenic influence on epithelial cells [2] where the interaction between the epithelial and stromal cells through paracrine and autocrine factors play an important role in these processes. Basic fibroblast growth factor (bFGF) plays an important role in mitogenic effects of androgens. bFGF was isolated in the prostate in the 1980s [3-5] and is a representative of different proteins family and has a powerful mitogenic effect on the prostate epithelial and stromal cells [2]. Later some other fibroblast factors (FGF1, FGF3, FGF7 and FGF8) were also isolated in the hyperplastic prostate. These factors possess mitogenic activity regarding prostate stromal and epithelial cells but the most vital factor stimulating prostate growth is bFGF which displays its effect in the prostate through FGFR1 and FGFR2 specific receptors [6]. In the healthy prostate only stromal cells express bFGF receptors. This shows the importance of bFGF for mesenchyme homeo-

stasis through stromal autocrine regulation. There were detected some other prostate growth factors stimulating prostate size growth. These are epidermal growth factors (EGFs) and transforming growth- α factor (TGF- α) [2]. On the other hand, there were also detected growth inhibiting factors whose prototype is a transforming growth factor- β 1 (TGF- β 1). TGF- β 1 is a multifunctional polypeptide which affects androgen independently, thus regulating proliferation and differentiation of epithelial cells, apoptosis, extracellular matrix formation and degradation [7]. It is specific that TGF- β 1 is produced by smooth muscle cells but TGF- β 1 receptors are also identified in epithelial and stromal cells. While affecting epithelial cells TGF- β 1 inhibits proliferation and stimulates the differentiation of basal cells into luminal ones but while affecting stromal cells TGF- β 1 stimulates their aggregation. TGF- β 1 is a key factor in stimulating apoptosis in which protease family has the leading role [8].

The basic fibroblast growth factor (bFGF) affects through paracrine/autocrine mechanism through high-affinity transmembrane receptors [9], thus displaying angiogenic and hematopoietic properties and stimulating many cells system proliferation. It has been established that bFGF stimulates stromal growth in the pros-

tate [10] and in the case of benign prostatic hyperplasia (BPH) in the gland tissues bFGF concentration exceeds 2-3 times its content in the normal gland tissues and bFGF receptors genes expression increases from 2 up to 8 times [11, 12].

According to the data by D.Giri and M.Ittmann [13] there is a bFGF double increase in the prostate tissues with BPH and bFGF is a powerful factor for both stromal and epithelial cells growth. bFGF concentration radioimmune definition revealed that in the case of BPH bFGF concentration is 2-3 times higher than in the normal prostate of elderly men [14]. Moreover, it has been revealed that there is no essential bFGF concentration difference in different zones and tissues of the prostate such as periurethral zones, stromal and epithelial tissues. However, according to F.Sciarra and co-authors [15] bFGF concentration in the prostate sections are still different: in periurethral zone tissues it is higher than in peripheral subcapsular zone and androgen concentration (dihydrotestosterone, testosterone) undergoes similar changes. A significant increase in genes expression has been revealed for bFGF with BPH in gland tissues compared with the normal prostate tissues, whereas aFGF transcription has not been observed except for one case. Epidermal growth factor (EGF) in the hypertrophic prostate has not been observed, either. TGF- β 2 expression, but not TGF- β 1 expression, rises whereas aFGF is not practically seen in the hyperplastic prostate tissues. Hence, it can be asserted that bFGF and TGF- β 2 are included in the BPH progression mechanism. bFGF and aFGF expressions were immunohistochemically defined in the BPH patient tissues after transurethral prostatectomy. It turned out that aFGF expression is absent both in basal epithelial cells and in the stromal compartment while bFGF expression was observed in cytoplasm of all the epithelial cells except for luminal ones. It must be pointed out that bFGF expression decreases in the regions with moderate epithelial displasia and intensive nuclear cytoplasmic bFGF expression is revealed in smooth muscle stromal cells [16, 17]. Based on the data at our disposal it can be assumed that bFGF is involved in BPH pathogenesis. In this respect bFGF and TGF- β 1 concentration in blood serum of the patients with BPH has been researched.

II. Material and methods.

208 patients with BPH aged 57-81 have been involved in the research at St.Grigor Lusavorich Medical Center in Yerevan in the period of 2000-2006. Urology examination included anamnesis study, residual urine and the prostate volume dimension by transabdominal ultrasonic scanning and urine and blood laboratory examination. Prostate-specific antigen (PSA) was found in the blood of all the involved patients.

Besides, all the patients underwent uroflowmetric examination. This examination revealed urine maximal flow rate (Qmax) and if Qmax was more than 15ml/s it was considered as a normal one. Urination parameters examination was carried out by comparing the uroflowmetric results data with the ones of healthy people.

For BPH symptoms quantity estimation the International Prostate Symptom Score (IPSS) has been used. IPSS was recommended by the First International Consultative Committee on BPH held under WHO aegis in Paris in 1991.

bFGF quantity definition in blood serum of the patients with BPH was assessed by immune analysis method worked out by R&D Systems Inc. (Minneapolis, USA) using Quantikine High Sensitivity Systems. This made it possible to define bFGF quantity both in blood serum and in urine even if its minimal revealed concentration is 0.05 pg/ml.

TGF- β 1 quantity definition in blood serum of the patients with BPH was carried out by immune analysis method worked out by R&D Systems Inc. (Minneapolis, USA) using Quantikine Human TGF- β 1 Immunoassay. This made it possible to define bFGF quantity both in blood serum and in urine even if its minimal revealed concentration is 3 pg/ml.

Blood serum samples received by the method recommended by National Committee for Clinical Laboratory Standards, USA were kept under $t \leq -20^\circ\text{C}$ before the research. Optical density definition was carried out on Multiscan Data Plasma Photometer (Thermo Electron Corporation, United Kingdom). Concentration quantization was done on a microcomputer Toshiba L10 using a WHO specially worked out program on immune analysis (WHO EISA Data Processing Program, version 5.2).

All the received results were compared with bFGF level in blood serum of healthy aged men without BPH (control group).

The results were also statistically processed by Student's method with t -criterion and P values less than 0.05 were not considered as a statistically important difference for the compared values.

III. Results and Discussion.

The results of the research made it possible to establish that bFGF concentration in blood serum of healthy young men is 1.61 ± 0.5 pg/ml. These data correspond to the data received by many other authors who established that bFGF concentration in blood serum of healthy men varies among 0.05 to 2.2 pg/ml [18]. It must be pointed out here that bFGF concentration determination in blood serum of healthy men is rather variable [19]. This fact is apparently conditioned by different research methods with different degrees of sensitivity and exactness.

Table 1

BPH patient groups based on bFGF concentration in blood serum

Patient group	bFGF average concentration in blood serum (pg/ml)
I	1.54 ± 0.6 (n = 45)
II	2.8 ± 0.3 (n = 25)
III	4.2 ± 0.5 (n = 26)
IV	5.9 ± 1.6 (n = 35)
V	16.4 ± 4.2 (n = 39)
VI	44.0 ± 10.8 (n = 38)

At present it is a well-known fact that the most exact and high-sensitive method to determine bFGF concentration in biological liquids, including blood serum as well, is the immune-enzyme analysis with the help of Quantikine HS FGF basic immunoassay kit (R&D Systems Inc., USA and United Kingdom) (Quantikine HS. Human FGF basic immunoassay for the quantitative determination of human fibroblast growth factor concentration in serum, plasma and urine. R&D Systems Inc., 2005).

BPH was revealed after a complex examination of the patients and bFGF concentration in blood serum varies at a rather large range among 0.9 and 68.9 pg/ml and the patients were formed into 6 groups according to bFGF concentration in blood serum (see Table 1).

It is worth mentioning that not all the patients with BPH have bFGF higher level in blood serum (Group 1)

compared with the control group (healthy men). The second group patients have a high bFGF level in blood serum which is equal to 73.9% ($p \leq 0.001$). The third group patients have 160% more with $p \leq 0.001$. The fourth and fifth groups respectively have 4 and 10 times more bFGF level in blood serum with $p \leq 0.001$. And finally the sixth group has bFGF level in blood serum 30 times more with $p \leq 0.001$.

All these data prove that bFGF concentration in blood serum of the patients with BPH is high in most cases: 153 patients which makes 73.5% of the examined patients, 134 patients (64.4%) have bFGF concentration in blood serum exceeding 4.2 pg/ml, an at last 38 patients (18.2%) with BPH have bFGF concentration in blood serum exceeding 40 pg/ml (See Table 2).

Our research results show that the basic TGF- β 1 concentration (pg/ml) in blood serum of the patients with

Table 2

TGF- β 1 average concentration in blood serum (pg/ml) of the patients with BPH (concentration decrease in % compared with the control group is given in the brackets)

Patient group	TGF- β 1 average concentration in blood serum (pg/ml)
I	19.1 ± 2.2 (- 32.3% . $p < 0.05$)
II	12.9 ± 1.9 (- 54.2 % . $p < 0.05$)
III	8.2 ± 1.9 (- 70.9 % . $p < 0.001$)
IV	6.2 ± 1.5 (- 78.0 % . $p < 0.001$)
V	4.1 ± 1.9 (-85.5 % . $p < 0.001$)
VI	3.5 ± 1.2 (-87.6 % . $p < 0.001$)

BPH is rather low compared with its concentration in blood serum of healthy men. For example, average TGF- β 1 concentration in blood serum of healthy men is 28.2 ± 3.4 pg/ml and varies from 22.7 to 42.8 pg/ml. However, it is rather lower for the patients with BPH (see Table 2). It is especially significant and statistically reliable that IV, V and VI group patients who have rather high bFGF concentration exceeding 0.05 pg/ml have a low TGF- β 1 concentration in blood serum as well and TGF- β 1 concentration reduction in blood serum is respectively 78.0%, 85.5% and 87.6% for the mentioned groups.

Special attention must be drawn to the fact that bFGF and TGF- β 1 basic concentrations in blood serum of all the six group patients with BPH are essentially different from each other and if TGF- β 1 concentration decreases bFGF concentration increases (Fig. 1).

So, our research results data revealed that bFGF and TGF- β 1 (bFGF / TGF- β 1) level correlation in the blood serum of the patients with BPH is significantly high compared with the same index of healthy men. This takes place because of both the increase of bFGF concentration and TGF- β 1 concentration reduction.

IV. Conclusion. Our research results data prove that bFGF basic level is essentially high and TGF- β 1 basic level is significantly low in blood serum of the patients with BPH compared with healthy men blood serum.

With respect to the above mentioned it must be pointed out that bFGF, i.e. the decrease of the initial level of one of the key stimulators of stromal fibromuscle pro-

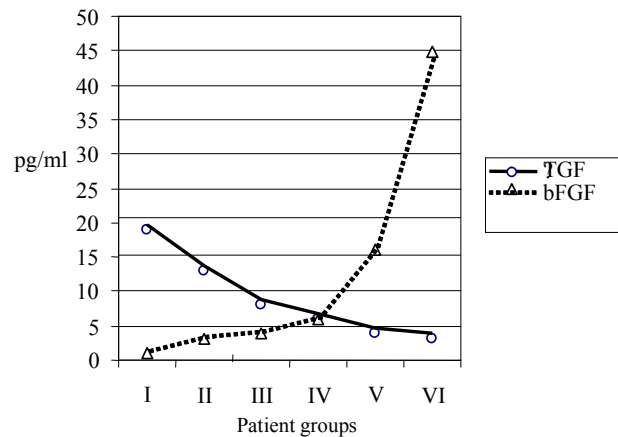


Fig. 1. bFGF and TGF- β 1 basic concentrations in blood serum of the patients with BPH in six groups.

liferation in the prostate is accompanied by a significant fall of β 1 transforming GF (TGF- β 1) which is the proliferation inhibitor and apoptosis inductor.

Such a disbalance between the concentrations of the two main factors involved in the stromal proliferation regulation in the prostate is possibly one of the main pathogenetic factors of BPH progression.

Based on the results of our survey it can be assumed that the discovery of peptide regulation role in the prostate growth is a perspective to work out some concepts for BPH antipeptidergic therapy by creating bFGF antagonists.

სამედიცინო მეცნიერებანი

ზრდის ფაქტორები კუთილთვისებიანი პროსტატული ჰიპერპლაზიით დაავადებული პაციენტების სისხლის შრატში

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(წარმოდგენილია აკადემიკოს ლ. მანაგაძის მიერ)

კვლევის მიზანი იყო კუთილთვისებიანი პროსტატული ჰიპერპლაზიით დაავადებული პაციენტების სისხლის შრატში ზრდის ფაქტორების კონცენტრაციის განსაზღვრა. მაღალი მგრძობელობის იმუნოლოგიური ანალიზით დადგინდა, რომ კუთილთვისებიანი პროსტატული ჰიპერპლაზიით დაავადებულ პაციენტებში

(ასაკი 57-81 წელი) ბაზური ფიბროპლასტის ზრდის ფაქტორის (ბფზფ) კონცენტრაცია უფრო მაღალია, ვიდრე საკონტროლო ჯგუფში (ჯანმრთელი მამაკაცები). ხშირ შემთხვევაში ბფზფ-ის კონცენტრაცია ($1,6 \pm 10,5$) ყ ($44,0 \pm 10,8$) pg/ml ფარგლებშია, მაშინ როდესაც β -1 გარდაქმნის ფაქტორის კონცენტრაცია დაბალია და იცვლება ($19,1 \pm 2,2$) ყ ($3,5 \pm 1,2$) pg/ml ფარგლებში.

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