

Original Paper

Zinc and Androgen Hormones in Benign Prostatic Hyperplasia

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REZUMAT

Relația zinc - hormoni androgeni în hiperplazia benignă de prostată

Hiperplazia benignă de prostată este una din cele mai frecvente cauze de adresabilitate către medicul urolog, datorită simptomatologiei care scade repede și vizibil calitatea vieții pacienților.

Obiective: Autorii au analizat statusul zincului și al hormonilor androgeni la pacienții cu hiperplazie prostatică cu scopul de a identifica o relație posibilă între metabolismul zincului și dezechilibrele hormonale în hipertrofia benignă de prostată.

Material și metodă: Studiul s-a bazat pe analiza observațională a 22 de bărbați cu hipertrofie benignă prostatică netratată la prim diagnostic și 30 de voluntari sănătoși, cu vârstă și profil biologic similar.

Rezultate: Au fost obținute diferențe semnificative statistic între bărbații cu hipertrofie benignă de prostată și grupul control, pentru: antigenul specific prostatic, zincul seric, raportul zinc ($\mu\text{g}/24\text{ h}$)/creatinină ($\text{mg}/24\text{ h}$). S-a obținut o relație negativă fără semnificație statistică între testosteron și antigenul specific prostatic la pacienții cu hipertrofie benignă de prostată ($r = -0.17$, $p > 0.05$) și o relație pozitivă cu semnificație statistică între dihidrotestosteron și antigenul specific prostatic ($r = 0.14$, $p < 0.05$). O corelație strânsă a fost observată între statusul zincului și nivelul hormonilor androgeni.

Concluzii: Relațiile dintre zincul seric și antigenul specific prostatic, testosteron, respectiv dihidrotestosteron sugerează o posibilă implicare a zincului în tulburările metabolice ale hormonilor androgeni la pacienții cu hipertrofie benignă de prostată.

Cuvinte cheie: hiperplazie benignă de prostată, zinc, testosteron, dihidrotestosteron

ABSTRACT

Benign prostatic hypertrophy is one of the most common causes of urological addressability because of the symptoms that rapidly and visibly decrease patients' quality of life.

Objectives: The authors analyzed zinc and androgen hormones status in patients with prostate disorders and

aimed at identifying a possible relation between zinc metabolism and hormonal disorders in benign prostate hypertrophy.

Material and methods: The study was based on the observational analysis of 22 untreated men with benign prostatic hypertrophy as first diagnostic, and 30 healthy volunteers, with similar age and biological profile.

Results: Statistical significant differences between men with benign prostatic hypertrophy and control group for: prostate specific antigen, serum zinc, zinc ($\mu\text{g}/24\text{ h}$)/creatinine ($\text{mg}/24\text{ h}$) ratio have been identified. A negative connection without statistical significance was obtained between testosterone and prostate specific antigen in patients with benign prostatic hypertrophy ($r = -0.17$, $p > 0.05$) and a positive connection with statistical significance between dihydrotestosterone and prostate specific antigen ($r = 0.14$, $p < 0.05$). A strong correlation was observed between zinc status and androgen hormones level.

Conclusions: The relations between serum zinc and prostate specific antigen, testosterone, respectively dihydrotestosterone in patients with benign prostatic hypertrophy suggested a possible implication of zinc imbalance in androgen hormones metabolism.

Key words: benign prostatic hyperplasia, zinc, testosterone, dihydrotestosterone

INTRODUCTION

Prostatic pathology represents one of the most common causes of dermato-urological addressability, because of the varied age interval, but also because of the symptoms that decrease rapidly and visibly the patients' quality of life.

Benign prostatic hypertrophy (BPH) is represented by increased volume of the prostate, which generates an obstructive and irritative symptomatology in the pelvic urinary tract. The hormonal influence presents a certain contribution in the development and evolution of BPH, by the imbalance occurred between androgens and estrogens, revealed by the significant decrease of the ratio androgens/estrogens hormones and by the inflammatory factors (1,2,3,4).

Zinc is a major part of metalloenzymes, having high concentrations in prostate. In the epithelial prostatic cells the absorption of zinc is influenced by the androgen hormones and by prolactin.

Also, it was observed that zinc plays an essential role in synthesis and secretion of LH (luteinizing hormone) and FSH (follicular stimulating hormone), acting on the testicular development, on seminiferous tubules, on spermatogenesis, on androgenic metabolism and on steroid receptors (5).

Zinc deficiency affects the level of prolactin, dopamine and acetylcholine in non-neuronal tissues, alters estrogen and androgen receptor expression, disrupts the balance between estrogens and androgens, stimulates or suppresses enzyme

systems (steroid dehydrogenase, aromatase, 5 alpha reductase) (Fig. 1).

Zinc (Zn) was considered after some researches a useful marker in non-bacterial chronic prostatitis diagnosis, while other studies did not find valid statistical correlations between the level of zinc in prostatitis and BPH compared to control group (6,7). A lot of studies documented the role of zinc in prostate physiopathology, but the results were controversial.

The authors analyzed zinc and androgen hormones levels in patients with prostate dysfunctions and tried to identify a possible correlation between zinc metabolism and hormonal disorders in benign prostate hypertrophy (1,5,6,7).

MATERIAL AND METHOD

The study was based on the observational analysis of 22 cases of untreated men with BPH as first diagnostic, and 30 healthy volunteers, followed during the years 2012-2013. The groups had similar age and biological profile (Table 1). All the patients signed the informed consent for inclusion in the study.

Exclusion criteria: patients with severe burns, with advanced chronic diseases, alcoholics, people with type 1 or 2 diabetes, with anorexia, vegetarian diet, malabsorption, acrodermatitis enteropathy, Wilson disease, fever, sepsis, myocardial infarction, estrogen therapy.

Hematological and biochemical parameters were evaluated with an automatic system, using

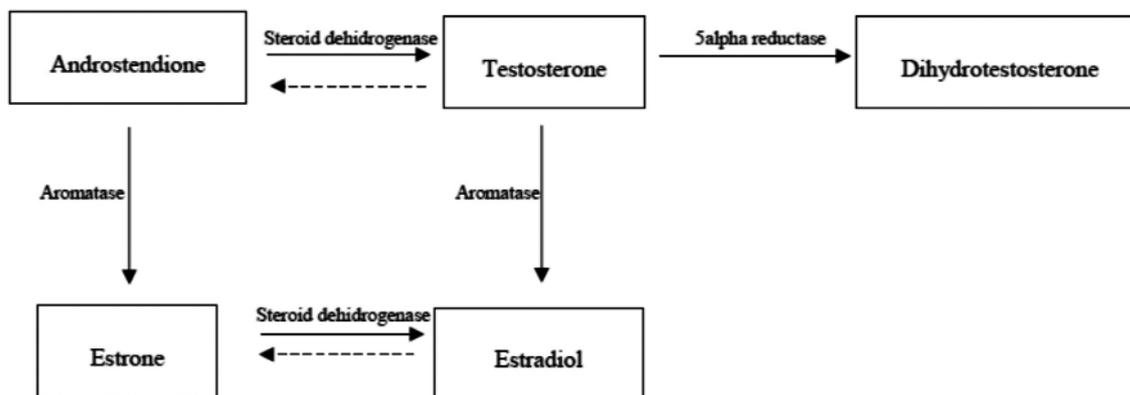


Figure 1. Major biosynthetic ways of sexual hormones

standardized methods of analyze. The microbiological and serological investigations were made according to standardized protocols of analyze.

Zinc was determined by spectrophotometric method with 5-Brom-PAPS monoreactive, based on the next principle: zinc forms with 2- (5- Bromine-pyridazolo)- 5- (N-propyl-N- sulfopropilamino)-phenol a red colored complex product. The absorbance at 560 nm was directly proportional with zinc concentration from the sample (8).

Table 1. The basal characteristics of the studied groups

Characteristics	BPH (n=22)	Control group (n=30)
Age (years)	61.3±12.8	56.2±10.7
Hemoglobin (g/dl)	13.7±0.6	13.9±0.7
Leukocytes (10/mm ³)	810±265	610±130
Thrombocytes (10 ³ /mm ³)	212±47	207±36
AST (U/l)	26.3±8.1	22.1±7.5
ALT (U/l)	24.1±6.4	19.4±6.2
GGT (U/l)	44.5±8.5	28.2±6.6
Prostatic phosphatase (U/l)	4.2±3.7	0.8±0.6
PSA (ng/ml)	5.2±4.1	0.9±0.7
CRP (mg/dl)	1.16±0.72	0.28±0.22
Urea (mg/dl)	50.8±25.3	29.7±8.2
Creatinine (mg/dl)	1.36±0.46	0.88±0.26
Zinc (µg/dl)	73.8±18.1	91.4±11.6
Zinc (µg/24 h)	665±204	440±95
Zn (µg/24 h)/ Creatinine (mg/24 h)	0.69±0.16	0.48±0.10
Testosterone (ng/ml)	3.24±1.06	3.97±1.72
Dihydrotestosterone (ng/ml)	418.6±123.5	376.12±119.2

The quantitative determination of testosterone was performed using chemiluminescence, and the determination of dihydrotestosterone was performed using ELISA test.

Biological samples were:

- 1) venous blood collected a jeun in vacutainers with anticoagulant (K3EDTA) for CBC;
- 2) venous blood collected in vacutainers without anticoagulant with or without gel separation for biochemical and serological investigations;
- 3) last 24 hours urine collected in plastic vessels and kept cold for parameters of interest (zinc and creatinine) dosage;
- 4) morning urine for urine culture in sterile vial and a suitable for urinalysis vial.

Statistical analysis consisted in the expression of all laboratory variables by mean value and standard deviation and also, finding the statistical correlations between studied groups using Pearson coefficient. Studied parameters were evaluated using the SPSS 20th version, an IBM software.

RESULTS

Benign prostatic hypertrophy was diagnosed using the parameters recommended in the European guidelines: anamnesis and IPSS (international prostatic symptomatology score), digital rectal examination, PSA, ultrasound (evaluation of the prostatic volume and post-voiding urine), evaluation of the renal function, uroculture. 22 men with BPH, with mean age of 61.3 years, met the inclusion criteria in the study.

The control group with mean age of 56.2 years was made of 30 healthy volunteers.

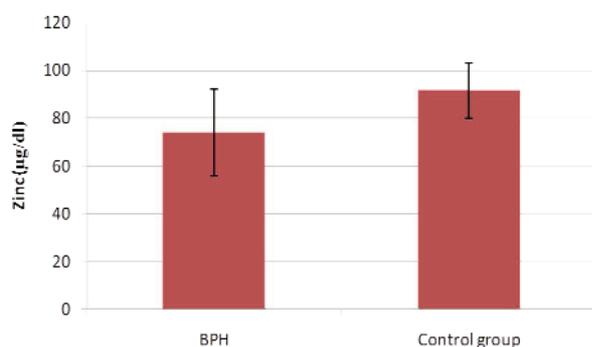


Figure 2. Serum level of zinc in men with BPH and control group

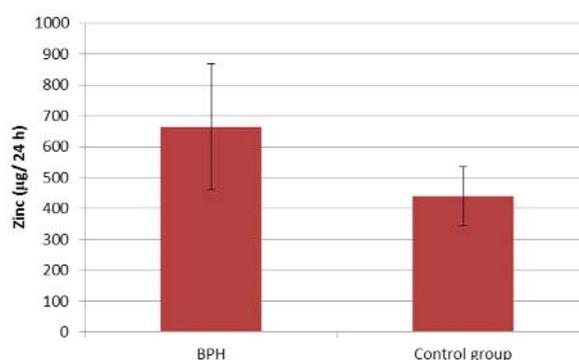


Figure 3. Urinary excretion of zinc in men with BPH and control group

In **Table 1** basal characteristics of participants at the study are presented: age, hematologic parameters (hemoglobin, leukocytes, thrombocytes), biochemical parameters (TGO, TGP, GGT, prostatic phosphatase, PSA, CRP, urea creatinine, zinc, and endocrine factors – testosterone and dihydrotestosterone). No statistical significant differences between patients with BPH and control group concerning the age, hematological, hepatic or renal tests have been identified. Statistical significant differences between men with BPH and control group for: PSA (5.2 ± 4.1 ng/ml in BPH, 0.9 ± 0.7 in control group, IC = 95%, $p < 0.05$), serum Zn (73.8 ± 18.1 µg/dl in BPH group from 91.4 ± 11.6 µg/dl in control group, IC= 95%, $p < 0.05$), zinc (µg/24 h)/ creatinine (mg/24 h) ratio (0.69 ± 0.16 in BPH from 0.48 ± 0.10 in control group, IC= 95%, $p < 0.05$) were observed. Mean value for serum zinc was 73.8 ± 18.1 µg/dl in BPH group and 91.4 ± 11.6 µg/dl in control group (**Fig. 2**). Urinary level of Zn was 665 ± 204 µg zinc/24 hours in BPH group and 440 ± 95 µg zinc/24 hours in control group (**Fig. 3**).

Zinc (µg/24 hours)/creatinine (mg/24 hours) ratio was 0.69 ± 0.16 in patients with BPH and 0.48 ± 0.10 in control group (**Fig. 4**).

No correlations were observed in the studied groups between zinc serum level and biological, hematological or biochemical parameters analyzed. Negative correlation was obtained - but with no statistical signification - between serum zinc and PSA ($r = -0.186$, IC= 95%, $p > 0.05$), between zinc (µg/24 h)/ creatinine (mg/24 h) ratio and prostatic phosphatase ($r = -0.097$, IC= 95%, $p > 0.05$) in patients with BPH.

The connection between variations of serum zinc and imbalance of androgen hormones received special attention. Testosterone showed significantly lower values in patients with BPH compared to

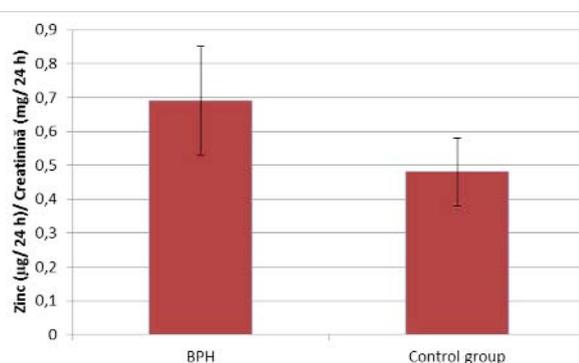


Figure 4. Variation of zinc (µg/24 h)/ creatinine (mg/24 h) ratio in men with BPH and control group

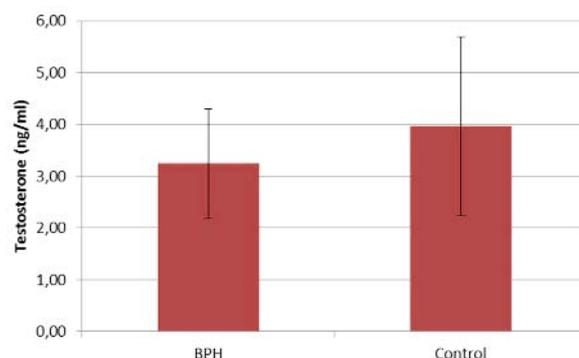


Figure 5. Serum level of testosterone in men with BPH and control group

control group (3.24 ± 1.06 ng/ml vs. 3.97 ± 1.72 ng/ml, CI 95 %, $p < 0.05$) (**Fig. 5**). DHT recorded significantly higher values in patients with BPH compared to control group (418.6 ± 123.5 ng/ml vs. 376.12 ± 119.2 ng/ml, CI = 95 %, $p < 0.05$) (**Fig. 6**). There was no significant correlation between variations of testosterone and DHT in the control group, instead, a negative association without statistical significance in patients with BPH ($r = -0.22$, $p > 0.05$) was

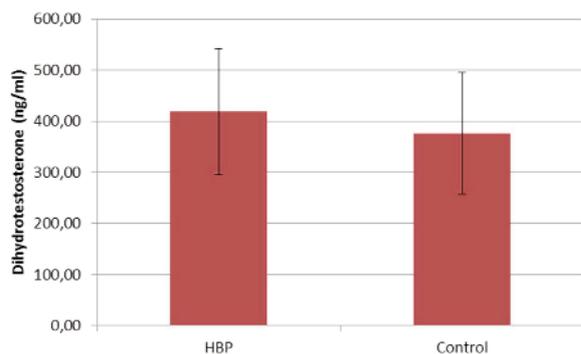


Figure 6. Serum level of dihydrotestosterone in men with BPH and control group

obtained. A negative connection without statistical significance between testosterone and PSA in patients with BPH ($r = -0.17$, $p > 0.05$) and a positive connection with statistical significance between DHT and PSA ($r = 0.14$, $p < 0.05$) were also identified.

It is important to pay attention to the statistical correlation between zinc and androgen hormones variation. Thus, between serum zinc and serum testosterone a statistical significant positive connection ($r = 0.46$, $p < 0.05$) was obtained. A negative connection with statistical significance was determined between serum zinc levels and DHT ($r = -0.29$, $p < 0.05$).

DISCUSSIONS

A lot of studies mentioned the importance of zinc in prostate physiopathology, showing its favorable action in modulating some enzymatic systems (5-alpha-reductase, aconitase, phosphomonoesterase), in testicular androgen metabolism, in organogenesis, in spermatogenesis, in transmethylation process, in immunity, in apoptosis (1,2,3,4).

In this study, the authors analyzed the variations of zinc in serum and urine in patients with BPH. Serum concentration of zinc in patients with BPH was significantly lower compared to control group (Fig. 1). This decreased blood levels of zinc could be, in authors opinion, a cause of a high elimination of zinc in urine (Fig. 2). According to this information, the authors granted diagnostic value to the decreasing of zinc concentration in blood in patients with BPH.

Also, it was observed the increasing of zinc ($\mu\text{g}/24\text{h}$)/creatinine ($\text{mg}/24\text{h}$) ratio in patients with prostatic pathology compared with control group (Fig. 3) and the existence of a negative correlation

between zinc and PSA, zinc/creatinine ratio and prostatic phosphatase. Those results argued for the analysis of a possible correlation between zinc status and hormonal imbalance in patients with BPH (Table 1).

An important interest of the authors is represented by the acknowledging of the problems caused by zinc deficiency in patients with BPH. This study demonstrated that zinc deficiency was associated with androgen hormones imbalance. Low serum zinc obtained in patients with BPH would compromise the neurohormonal balance, the balance of essential minerals in the body, the estrogen and androgen receptor expression in the prostate, determining disorders of stress-related gene expression.

The results of this study confirmed the importance of testosterone and dihydrotestosterone in BPH pathophysiology and the involvement of zinc in this disorder. In literature, there were no absolute statements concerning the correlation between zinc and the severity of the prostatic pathology.

Our results were in line to some recent reports that mentioned a decreasing in tissue zinc, a significant decreasing of serum zinc and an increasing of zinc excretion in BPH, compared with normal tissues (9,10).

Other studies related an accumulation of tissue zinc in BPH (6). Zinc deficiency in patients with BPH could have a role in apoptosis by regulation of Bcl-2, BAX, p-65, NFkB expression (1,2,3,4,6).

Zinc supplementation (11,12) could reduce the risk of developing BPH by regulation of hyperplastic cell growth, by modulating the mitochondrial aconitase activity and by regulation of the citrate level in prostatic cell, by reducing the estrogen level, by reducing the prolactin formation, by inhibiting 5-alpha reductase and by reducing dihydrotestosterone synthesis, by regulating mitochondrial apoptosis (translocation of c cytochrome from mitochondria in cytosole, 3 and 9 caspase activation, PPAR cleavage) (2,3,4,13,14).

CONCLUSIONS

In our study, BPH was associated with an important reduction of serum zinc and a destabilization of the ratio between testosterone and dihydrotestosterone. The negative relation between serum zinc and PSA, between zinc and DHT in patients with BPH suggest a possible implication of zinc imbalance in androgen hormones metabolism.

In conclusion, the study of correlations between zinc, variation of androgen hormones and prostatic pathology remains a theme open for debate.

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