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Hormone concentration, metabolic disorders and immunoexpression of androgen and estrogen-alpha receptors in men with benign prostatic hyperplasia and testosterone deficiency syndrome

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Abstract

Introduction. A slight decrease in blood testosterone level in men is a physiological state associated with the aging. The aim of our study was to evaluate the occurrence of hormone and metabolic disorders, as well as the immunolocalization and immunoexpression of androgen receptors (AR) and estrogen-alpha receptors (ERα) in the prostates of men with benign prostatic hyperplasia (BPH) and coexisting testosterone deficiency syndrome (TDS).

Material and methods. The study involved 150 men, diagnosed with and receiving pharmacological treatment for BPH. Concentrations of glucose, total cholesterol (TCh), high-density lipoproteins (HDL), low-density lipoproteins (LDL), and triglycerides (TG) were determined in blood serum. Serum concentrations of total testosterone (TT), free testosterone (FT), estradiol (E2), luteinizing hormone (LH), insulin (I), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), and insulin-like growth factor 1 (IGF-1) were measured by ELISA. The number of AR-positive cells and ERα-positive cells were measured in prostate sections of men with BPH.

Results. Patients eligible for transurethral resection of the prostate and TDS were significantly more likely to have higher abdominal circumference and higher serum levels of insulin and IGF-1 as well as lower levels of FT and SHBG than control subjects with BPH and no TDS. Quantitative analysis revealed 35.8% AR-positive columnar epithelial cells and 24.3% AR-positive stromal cells in prostates of BPH patients with TDS and 30.5% and 23.0%, respectively, in BPH patients without TDS. However, the differences between the study and the control groups were statistically not significant. In prostates of BPH patients with TDS the immunoexpression of ERα was observed in 2.88% of the columnar epithelial cells and 0.39% of stromal cells. In BPH patients without TDS ERα-positive cells were only found in 0.04% of columnar epithelial cells and 0.62% of prostatic stromal cells.

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Conclusions. Considering the statistically significantly higher levels of I and IGF-1 and larger abdominal circumference of men with BPH and TT deficiency, it can be supposed that visceral obesity and carbohydrate disorders may contribute to the reduction of testosterone concentration. The results of our study indicate a relationship between TT concentration in the plasma of patients with BPH and the percentage of AR-positive cells in the prostate. *(Folia Histochemica et Cytobiologica 2015, Vol. 53, No. 3, 227–235)*

Key words: testosterone deficiency syndrome; benign prostatic hyperplasia; insulin; IGF-I; AR; ERα; IHC

Introduction

The development of prostate begins as early as the eight week after fertilization, and is determined by testosterone synthesis in the testes. The growth and function of the prostate gland are stimulated by dihydrotestosterone (DHT) [1], which acts through androgen receptors to induce the expression of the genes associated with the synthesis of growth factors [2, 3].

Benign prostatic hyperplasia (BPH) is a commonly occurring disease among elderly men. It is characterized by the proliferation of epithelial and stromal cells, followed by enlargement of the gland [3, 4] leading to frequent micturition, difficulties in initiating micturition, nycturia, a poor stream of urine, and a prolonged duration of micturition [4]. BPH can in this way lead to lower urinary tract symptoms (LUTS), causing a significant decline in the quality of patients' life [6]. The aging of developed societies will result in an increasing number of men affected by this problem. Approximate data suggests that by the year 2025, about 50 million Americans will suffer from BPH symptoms [7], which in turn will raise healthcare expenses [8, 9].

So far, the etiology of BPH has not been fully explained [10]. The process of the disease development is complex and related to many factors. Currently, we know of several etiological factors, of which hormonal disorders play an important role [9–12]. Androgens are essential for maintaining normal morphology and the function of the prostate [12, 13]. Testosterone and the product of its enzymatic transformation, dihydrotestosterone, undeniably take part in the growth and proliferation of prostate cells [14, 15].

A slight decrease in blood testosterone level in men is a physiological state associated with the aging. However, the decline in the level of testosterone observed in BPH, accompanied by coexisting metabolic disorders, is a controversial issue. The aim of our research was to assess the occurrence of hormone and metabolic disorders, as well as immunolocalization and immunoexpression of androgen receptors (AR) and estrogen-alpha receptors (ERα), in the prostates of men with BPH and coexisting testosterone deficiency syndrome (TDS).

Material and methods

Patients. The study involved 150 men aged 52–75 years (67.33 ± 8.28, mean ± SD), who received pharmacological treatment for BPH. The patients were qualified for planned transurethral resection of the prostate (TURP) at the Clinic of Urology and Urological Oncology at the Pomeranian Medical University in Szczecin, Poland.

TDS was diagnosed according to the guidelines of the International Society of Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), the European Association of Urology (EAU), the European Academy of Andrology (EAA), and the American Society of Andrology (ASA) 2000 [16]. BPH patients with total testosterone (TT) level below 2.5 ng/mL, or between 2.5 and 3.5 ng/mL, having clinical symptoms of 'low testosterone syndrome' assessed with Morley's ADAM (Androgen Deficiency in Aging Men) questionnaire [17], were classified into the group with TDS.

The study group consisted of 54 men diagnosed with both BPH and TDS. The control group consisted of 96 patients with BPH but without TDS, according to the above criteria. BPH patients were treated with 5-alpha reductase inhibitor (finasteride, orally, 5 mg daily). Patients with active alcoholism, thyroid or liver diseases, and active cancerous disease were excluded from the study.

The study was conducted with the consent of the Bioethical Commission of Pomeranian Medical University in Szczecin (permission number KB-0012/132/12). The patients were informed of the purpose and course of the study, and gave their written consent to take part in it.

Clinical examination. In both the study and the control groups, measurements of abdominal circumference, body weight, height, and blood pressure were made. The following metabolic parameters in blood serum were determined using standard methods: fasting blood glucose levels and the levels of total cholesterol (TCh), high-density lipoproteins (HDL), low-density lipoproteins (LDL), and triglycerides (TG).

An enzyme-linked immunosorbent assay (ELISA) method was employed to determine the levels of TT, free testosterone (FT), estradiol (E2), luteinizing hormone (LH), insulin (I), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), and insulin-like growth factor 1 (IGF-1).

The patients completed Morley's ADAM screening questionnaire for androgen deficiency in aging males [17].

Laboratory measurements. To determine the metabolic parameters, 9 mL fasted blood samples were collected from a cubital vein. The serum was stored in Eppendorf test tubes in a freezer at a temperature of –20°C for no longer than three months. The levels of metabolic parameters were determined by means of a spectrophotometric method using pre-developed assay reagent kits (Biolabo, Aqua-Med, Lodz, Poland). Hormone levels were determined with the ELISA method using pre-developed assay reagent kits (DRG Medtec, Warsaw, Poland).

Immunohistochemical analysis. To determine the immunolocalization and immunoexpression of AR and ERα in the prostates of men with BPH, the prostate sections were deparaffinized and hydrated with various concentrations of alcohol, in descending order. The sections' preparations were then heated for 30 min in a water bath at a temperature of 96°C in Target Retrieval Solution buffer of pH 9.0 (Dako, Glostrup, Denmark). Endogenous peroxidase activity was blocked with Peroxidase Blocking Solution (Dako) for 10 min in a humidified chamber at room temperature. The sections were incubated for 30 min in a humidified chamber with the following monoclonal primary antibodies diluted in provided solution (Dako): Monoclonal Mouse Anti-Human Androgen Receptor Clone (1:50, Dako) and Monoclonal Mouse Anti-Human Estrogen-α Receptor Clone (1:50, Dako).

The sections were then incubated with a secondary antibody linked to horseradish peroxidase (Dako REAL™ EnVision™ Detection System Peroxidase/DAB+, Rabbit/ /Mouse, Dako). 5,5'-diaminobenzidine (DAB) was used to visualize the immunohistochemical reaction (Dako). The sections were counterstained with Mayer's hematoxylin. After each step, the slides were rinsed with phosphate-buffered saline (PBS). The sections were dehydrated and closed in the medium Histokitt (Mar-Four, Lodz, Poland). The preparations were assessed using a light microscope (BX 41, Olympus Optical, Tokyo, Japan).

The number of AR-positive cells and ERα-positive cells detected by immunohistochemistry were separately counted in prostate sections of patients. Ten fields of vision (at a total magnification of ×400) were assessed in 15 section for each evaluated prostate of 25 men from the study (BPH with TDS) group and 25 men from the control (BPH) group. The results were shown as a percentage of AR-positive and ERα-positive cells, compared to all stromal cells and all columnar epithelial cells of the prostate assessed in the field of vision.

Statistical analysis. Statistical analysis was performed using SPSS Statistics 14.0 (Chicago, IL, USA). Basic statistics were used for the study and the control groups. The distribution's normality was examined using a Shapiro-Wilk test. Statistical analyses were performed using the Mann-Whitney U-test and, when appropriate, Student's t-test. Moreover, the data measured on dichotomous scales were analyzed using a chi-square test of independence with Yates' correction. Correlations between the parameters were analyzed using Pearson's correlation coefficient. It has been assumed that there was no correlation for correlation coefficients of 0.0–0.2, weak correlation for 0.2–0.4, moderate correlation for 0.4–0.6, strong correlation for 0.6–0.8, and very strong correlation for ± 0.8–1.0. The level of significance was set at $p < 0.05$.

Results

Clinicopathologic characteristics of patients

Data presented in Table 1 show that BPH patients with TDS eligible for transurethral resection of the prostate were significantly more likely to have higher abdominal circumference and serum concentrations of insulin and IGF-1, and lower levels of free testosterone and SHBG than control BPH patients without TDS.

No statistically significant differences in the frequency of clinically important disorders were found between patients with BPH and TDS or BPH patients without TDS (Table 2).The mean values of systolic and diastolic blood pressure were within normal range and did not differ between the study and control groups.

Hypertension was diagnosed according to criteria of European Society of Hypertension and European Society of Cardiology [18]: systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or treatment of previously diagnosed hypertension.

The analysis of the coexisting disorders showed that patients with BPH and TDS did not differ from patients with BPH and no TDS in respect to the incidence of pharmacologically treated hypertension (60.32% *vs.* 55.17%), hypercholesterolemia (33.33% *vs.* 36.78%) or diabetes (28.57% *vs.* 20.69%).

Serum concentrations of metabolites and hormones

The study group consisted of 54 men with a diagnosis of BPH and TDS, and a control group of 96 patients with BPH but without TDS. Patients with BPH and TDS were significantly more likely to have higher abdominal circumference and increased serum levels of insulin, IGF-1 and lower levels FT, SHBG than the controls with BPH but no TDS (Table 1).

The analysis of data of patients with BPH and with TDS demonstrated weak and moderate correlations between some parameters (Table 2). Abdominal

Table 1. Anthropometric parameters and concentrations of metabolites and hormones in patients with benign prostatic hypertrophy (BPH) and testosterone deficiency syndrome (TDS) and with BPH without TDS

	Patients with BPH and TDS (n = 54)		Patients with BPH and no TDS (n = 96)		P value
	Mean± SD	Range (min–max)	Mean± SD	Range (min–max)	
Age [years]	65.01 ± 6.43	54–75	65.21 ± 6.32	52–75	0.666
Body weight [kg]	87.76 ± 14.44	62–120	81.11 ± 14.54	51.5–165	0.074
Height [cm]	173.58 ± 8.42	153–198	172.82 ± 6.37	154–190	0.895
BMI [kg/m^2]	29.15 ± 4.49	18.72–39.18	26.79 ± 3.59	19.15–18.19	**0.035**
Abdominal circumference [cm]	103.04 ± 9.9	80–123	97.02 ± 8.47	79–125	**0.005**
Serum concentrations of metabolites and hormones					
Glucose (70–100 mg/dL)	117.11 ± 48.74	74–357	106.98 ± 29.62	77–329	0.238
HDL (35–70 mg/dL)	32.96 ± 9.01	20.7–60.27	36.27 ± 10.8	21.43–74.97	0.091
TG (50–200 mg/dL)	163.99 ± 91.32	67.27–609.09	136.13 ± 58.56	57.42–476	0.181
TCh (150–200 mg/dL)	187.08 ± 57.95	83.79–336.43	192.52 ± 59.75	100.75–454.86	0.658
LDL (< 135 mg/dL)	121.32 ± 52.06	18.1–261.01	129.68 ± 58.79	38.99–405.31	0.751
TT (2.6–11 ng/mL)	2.15 ± 0.12	0.09–3.42	5.13 ± 0.14	2.76–8.83	**p < 0.01**
FT [pg/mL]	68.8 ± 46.5	0.9–247.6	128.5 ± 72.8	20.3–367.6	**p < 0.01**
LH (2–9 mIU/mL)	11.21 ± 10.42	0.7–67.98	11.12 ± 4.56	3.29–24.99	0.270
SHBG (20–60 nmol/L)	29.6 ± 15.98	2.74–72.91	41.23 ± 19.59	2.58–98.03	**p < 0.01**
E2 (12–75 pg/mL)	31.08 ± 35.16	5.71–237.71	30.51 ± 25.4	4.93–168.83	0.475
DHEAS (1.1–4.7 μg/mL)	1.23 ± 0.71	0.04–3.44	1.16 ± 0.72	0.12–3.1	0.893
Insulin (15–180 pmol/L)	207.93 ± 175.22	18.47–784.02	116.60 ± 147.23	3.05–698.66	**0.002**
IGF–1 [ng/mL]	143.13 ± 63.96	41.97–351.1	116.47 ± 35.92	41.58–207.7	**0.035**

Abbreviations: BPH — benign prostatic hyperplasia, TDS — testosterone deficiency syndrome, BMI — body mass index, HDL — high-density lipoprotein, TG — triglycerides, TCh — total cholesterol, LDL — low density lipoprotein, TT — total testosterone, FT — free testosterone, E2 — estradiol, LH — luteinizing hormone, I — insulin, SHBG — sex hormone binding globulin, DHEAS — dehydroepiandrosterone sulfate, IGF-1 — insulin-like growth factor 1. Laboratory reference values for men are provided in parentheses. Statistically significant differences between compared groups were analyzed by Mann-Whitney U-test or Student's t-test

circumference correlated weakly negatively with SGHB level, and the latter correlated weakly negatively with IGF-1 level. Serum glucose concentration strongly correlated with serum TG level. The level of E2 correlated weakly negatively with the levels of TCh and LDL, and positively with the level of FT. Serum FT level correlated moderately positively with the TT and DHEAS concentrations. We found week correlation between TCh and DHEAS levels and a negative correlation between IGF-1 and SHBG concentrations (Table 2).

In the group of patients with BPH but without TDS (the control group), there was a weak positive correlation between abdominal circumference and serum levels of IGF-1 and TG (Table 3) and a weak negative correlation in respect to SHBG and HDL concentrations. Serum glucose concentration correlated weakly negatively with a decrease in the levels of LDL, TCh, and FT levels and moderately positively with TG concentration. The levels of TG correlated weakly positively with IGF-1 concentration and weakly negatively with TT levels. Total testosterone concentration correlated weakly with free testosterone level and moderately with SHBG concentration. The serum level of free testosterone correlated strongly with estradiol and moderately with DHEAS concentrations. LH level correlated weakly positively with SHBG and weakly negatively with IGF-1 concentrations. Insulin levels correlated moderately positively with IGF-1 concentrations (Table 3).

Immunohistochemical expression of androgen and estrogen-α receptors

The immunohistochemical analysis demonstrated differences in the expression of AR and ERα in the nuclei of columnar epithelial and stromal cells of prostate between the study group and the control group. The microphotographs documenting the expression of AR and ERα are shown in Figure 1.

Table 2. Selected correlations between measured parameters in patients with BPH and diagnosed with TDS

Correlated parameters for 54 subjects		Significance	Correlation coefficient
Abdominal circumference	SHBG	0.016	–0.331
Glucose	TG	$p < 0.01$	0.695
Diastolic blood pressure	TG	0.028	0.299
Diastolic blood pressure	TCh	0.003	0.399
Diastolic blood pressure	LDL	0.012	0.341
Diastolic blood pressure	FT	0.031	–0.295
TCh	E2	0.009	–0.353
LDL	E2	0.010	–0.350
TT	FT	$p < 0.01$	0.529
FT	E2	0.035	0.287
FT	DHEAS	0.003	0.403
TCh	DHEAS	0.039	0.281
SHBG	IGF-1	0.043	–0.366

Abbreviations as in the description of Table 1. Statistical significance was considered at $p \leq 0.05$

Table 3. Selected correlations between measured parameters in patients with BPH and no evidence of TDS

Correlated parameters for 96 subjects		Significance	Correlation coefficient
Abdominal circumference	SHBG	0.010	–0.263
Abdominal circumference	IGF-1	0.029	0.308
Abdominal circumference	TG	$p < 0.01$	0.355
Abdominal circumference	HDL	0.027	–0.226
Abdominal circumference	Glucose	0.003	0.297
Glucose	LDL	0.022	–0.236
Glucose	TG	$p < 0.01$	0.471
Glucose	FT	0.022	–0.236
Glucose	TCh	0.014	–0.254
TG	TT	0.050	–0.203
TG	IGF-1	0.027	0.312
TT	FT	0.002	0.318
TT	SHBG	$p < 0.01$	0.488
FT	E2	$p < 0.01$	0.653
FT	DHEAS	$p < 0.01$	0.459
LH	SHBG	0.007	0.277
LH	IGF-1	0.026	–0.316
Insulin	IGF-1	0.001	0.534

Abbreviations as in the description of Table 1. Statistical significance was considered at $p \leq 0.05$

The quantitative analysis revealed that patients with BPH and TDS did not differ from patients with BPH and no TDS in respect to the percentage of AR-positive columnar epithelial cells (35.79% *vs.* 30.45%) and AR-positive stromal cells (24.32% *vs.* 22.98%) of the prostate gland.

There was a weak immunoexpression of the estrogen-α receptor in prostate, both in columnar epi-

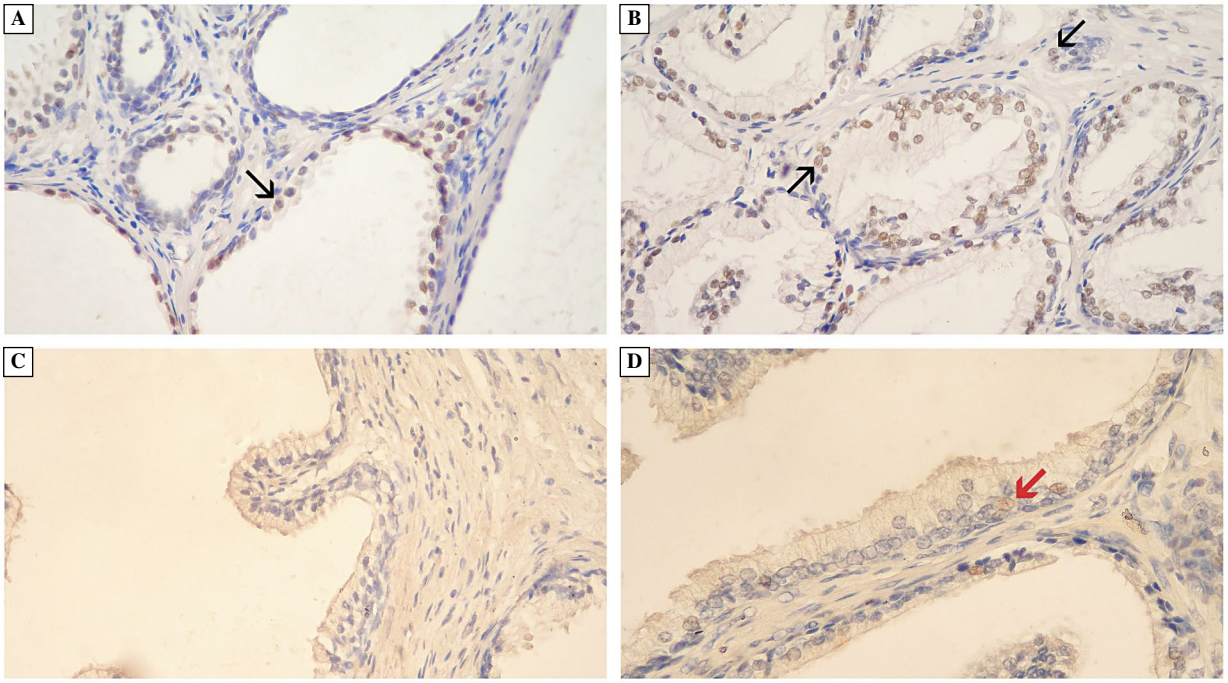

Figure 1. Immunolocalization and immunoexpression of androgen (A, B) and estrogen-α (C, D) receptor in prostate of patients with benign prostatic hyperplasia (BPH) and no evidence of testosterone deficiency syndrome (TDS) (A, C) or with BPH and TDS (B, D). Weak (A) or strong (B) immunoexpression in the nuclei of columnar epithelial cells (black arrow) and in the stromal cells (red arrow). Lack of immunoexpression of estrogen-α receptor in cell nuclei (C), and immunoreactivity present in several nuclei of columnar epithelial cells (black arrow) (D); scale bar — 20 μm

thelial cells and stromal cells in the study and control groups. In prostates of BPH patients with TDS, the immunoreactivity of ERα was observed in 2.88% of the columnar epithelial cells and 0.39% of stromal cells. In prostates of BPH patients without TDS, ERα-positive cells were only found in 0.04% of the columnar epithelial cells and 0.62% of stromal cells. However, the differences between study and control groups were statistically not significant.

Discussion

Testosterone deficiency syndrome is associated with a decline in androgen serum levels, and may lead to numerous clinical symptoms [19]. The most typical symptoms include reduction in the sex drive, worsening of physical and mental state, hair loss, and decline of muscle strength and bone mass [20].

Our results demonstrate that TDS is a common health problem among men with BPH, and that hormone and metabolic disorders may differ depending on testosterone levels. In our study, abdominal circumference in patients without TDS correlated positively with IGF-1, TG, and glucose levels, but such correlations were not observed in patients with TDS. A negative correlation between abdominal circumference and SHBG levels was noted both in the study and control groups. Analysis of the data shows that slight increases in the levels of triglycerides, total cholesterol, and LDL, along with a decrease in the level of FT, were accompanied by an increase in diastolic blood pressure in patients with TDS and BPH.

The role of estrogens in the regulation of the male reproductive system is increasingly better understood. The peripheral aromatization of testosterone is a major source of estrogens in men [21]. With age, the serum estradiol level either remains the same or increases, resulting in higher ratios of estradiol to testosterone [22]. In our study the ratio of E2 to TT is 0.07 in study group and 0.17 in control group. Investigations on animals confirm that changes in the physiological ratio of both hormones contribute to a gradual increase in the prostate volume and disturbances in urination [23]. Nevertheless, the study of Bernoulli et al. [23] fails to confirm the hypothesis that a decrease in the ratio of testosterone to estradiol is associated with LUTS. However, Tao et al. [24] found that patients with BPH had higher estradiol levels than patients without BPH. Our results suggest that

there is a relationship between the levels of estradiol and FT, both in BPH patients with and without TDS.

In our study, a positive moderate correlation between the levels of DHEAS and FT was found in both the study and control groups. This may be caused by the fact that both DHEA and DHEAS can be substrates in the process of biosynthesis of estrogen and testosterone [24]. Schatzl et al. [25] analyzed the relationships between hormone levels depending on the malignancy of pathological changes in the prostate. The levels of estradiol in this study were lower in patients with prostate tumors than in those with BPH/LUTS. However, no significant relationships between the levels of DHEAS and testosterone in both groups were found.

Insulin-like growth factor 1 (IGF-1) is a single-chain polypeptide hormone that can influence the growth, differentiation, and survival of cells. There is a hypothesis that IGF-1, which is structurally similar to insulin, may bind the same receptors and activate pathways implicated in the growth and proliferation of prostate cells. Moreover, some studies imply that elevated blood insulin levels are associated with higher activity of the sympathetic nervous system, and may increase prostate smooth muscle tension [26]. An *in vitro* study by Siejka et al. [27] demonstrated that pharmacological blockade of the action of growth factors may suppress the proliferation of human BPH cells.

The immunohistochemical results presented here show that AR-positive cell nuclei are more often found in the columnar epithelial cells and stromal cells of BPH patients with TDS than in BPH patients without TDS. The assessment of ERα immunoexpression reveals that the much higher incidence of these receptors is found in the columnar epithelial prostatic cells of men with BPH and TDS than in BPH patients without TDS.

There are many theories which prove the influence of testosterone and differences in AR expression in BPH. In normal prostate and BPH specimens AR are located in the nuclei of luminal epithelial cells, stromal cells, and basal epithelial cells [28]. Testosterone and other androgens as well as AR are important prostatic growth factors. They are necessary for maintenance of normal structure of prostate and were found to stimulate epithelial proliferation in castrated animals. Prostatic over-expression of epithelial AR in an animal model increased cellular proliferation [29]. There are also reports about growth-promoting role of AR and testosterone. Loss of AR-positive epithelial cells in conditional knockout animals and tissue recombinants results in increased epithelial proliferation and inhibition of prostate differentiation [30, 31]. The recent study of Wen et al. [32] showed that androgen receptors located in the prostate stroma may take part in the etiology of BPH. The immunohistochemical analysis of androgen receptors in BPH patients treated with finasteride conducted by Bauman et al. [33] suggests that this treatment may decrease the expression of this receptor in the prostate epithelium. Biolchi et al. [34] analyzed genotypes and testosterone levels in a group of 126 patients, aged 40 to 60 years, whose prostate volumes exceeded 30 mL. They demonstrated that the presence of a high number of repetitions of GGC in the gene encoding AR, as well as a lower testosterone level, predispose to a higher risk of BPH.

Estrogen-alpha receptors act comprehensively in both the female and male reproductive systems [35]. It has been suggested that the development of BPH in men may be related to the direct action of estradiol, *e.g.* due to the aromatization of androgens to estrogens which then bind to ERs in prostate and bladder [36]. This hypothesis was analyzed in men older than 40 years with BPH and other LUTS by Schatzl et al. [37] who showed that increased estrogens levels correlated closely with prostate hyperplasia, while increased serum testosterone level did not. There are reports on the activity of selective ER modulators, which *in vivo* reduced proliferation of human prostatic cells and initiated apoptosis and anti-inflammatory processes [38]. The results of these studies underline the special role of ERs as factors that are potentially important in BPH therapy [39]. However, the role of E2 in the prostate is not clear. Prins et al. suggested that estrogen imprinting and prostate pathologies are mediated by ERα of the stromal cells [40]. In normal prostatic cells ERα is found primarily in the nuclei of stromal cells; however, ERα is also found in epithelial cells [41]. The studies of Ricke et al. showed that in estrogen-treated male mice, the number of ERα-positive cells in the prostatic epithelium increased, while the number of ERα-positive epithelial cells decreased. This suggests that estrogens may mediate proliferation of prostatic epithelium. ERα is necessary for the proliferation of prostatic cells in estrogen-treated mice [41]. Thus, the role of E2 in BPH remains to be elucidated.

Determining the relationship between BPH and TSD, changes the levels of other hormones, metabolic disorders could have important therapeutic implications for the treatment of diseases of aging in men. Considering the higher levels of insulin and IGF-1 and larger abdominal circumference of men with BPH and TDS, it can be supposed that visceral obesity and carbohydrate disorders may contribute to the reduction of serum testosterone concentration.

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