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Changes in the level of cytokines among patients with prostate cancer after orchiectomy

Short Title: Effects of testosterone on cytokines

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Summary

Fourteen patients with cancer of the prostate of the 3-4 stage were held under examination. The ages of the patients ranged from 60-79. In all patients 1 month after an orchiectomy the levels of the following were measured in the serum of the blood: lutenizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, somatropic growth hormone (STH), testosterone, 17β-estradiol (E_2), estrone, 5α-dihydrotestosterone, insulin, 25-OHVitD$_3$, main fibroblast growth factor (bFGF), epidermal growth factor (EGF), transforming growth factor-β (βTGF), insulin-similar growth factor-1 (IGF-1), PSA, interlukin 1β (IL-1β), tumor necrosis factor α (TNFα), acid phosphatase, alkaline phosphatase, and Ca^{++}. Upon initial tests the average indicators of IL-1β, acid phosphatase, alkaline phosphatase, TNFα, and PSA had increased, while the indicators of testosterone and βTGF had decreased. A month after orchiectomy all patients showed a significant decrease in levels of testosterone, 5α-dihydrotestosterone, 17β-estradiol in comparison to initial indicators, while levels of LH and FSH had increased. The reduction of testosterone was accompanied by a statistically meaningful increase of prolactin, STH, and estrone. The reduction of 5α-dihydrotestosterone determined the reduction of EGF. The decrease in the level of testosterone was accompanied by a statistically significant increase in the levels of insulin, IGF-1, bFGF, 25-OHVitD_3, and Ca^{++} as well as by a reduction in the levels of βTGF, IL-1β, TNFα, acid phosphatase, alkaline phosphatase and PSA. Thus, as the level of testosterone after orchiectomy decreased, an increase in the level of factors that raise kariomitotic activity was observed, while a decrease in the level of factors regulating the cell cycle and attack of apoptosis was observed. Furthermore, a decrease in the indicators of anti-tumor cell immunity was observed.

Introduction

The androgen blockade method has been widely used during treatment of prostate cancer for more than 60 years (Petrylak, 2002). As a rule, establishment of the diagnosis of prostate cancer constitutes an androgen-dependent process and as a result of the androgen blockade tumor regression is observed among 70-80% patients. Therefore, it is considered that the main task of conservative therapy of prostate cancer lies in restricting the influence of androgens on the prostate gland. This is achieved with the help of preparations that block the stimulation of the formation of testosterone by the testicles on the level of the hypothalamic-hypophysis, with the help of anti-androgens, orchiectomy, or various combinations of these methods (Stepanov et al., 2000). However, a few years after the start of hormonal therapy the majority of patients show the development of low-differentiated androgen-resistant prostate cancer (Pummer, 2002).

The probability of development of prostate cancer significantly increases after forty years of age (Pushkar, 2002); from this period a decrease of testosterone circulating in the blood is observed in men. This decrease was named "partial androgen deficiency of aging men" (PADAM) (Bremner et al., 1983; Gray et al., 1991). PADAM provokes a breach of the mechanisms of regulation in the system of the gonads-hypophysis-hypothalamus, inciuding of an increase in the activity of the hypophysis (Vermuelen et al., 1998), as well as an increase of 5α-dihydrotestosterone and 17β-estradiol (Pechersky et al., 2002). The given factors exert a significant influence on the development of prostate cancer (Lopatkin et al., 1998).

The contradiction which arises when applying an androgen blockade lies in the fact that men with prostate cancer are prescribed therapy which, in addition to the breach of production of testosterone due to age, reduces the action of androgens on the prostate tissues.

Thus the prescription of antiandrogens only intensifies the consequences of the age-related decrease of testosterone, and doesn't eliminate ethiological and all pathogenetic factors of the development of prostate cancer. The given therapy is accompanied by a series of complications the most dangerous of which are changes in the heart-vasculatory system (Neri, Kassem, 1984; Lund, Rasmussen, 1988; Mickshe, 1990).

Materials and Methods

Patients

Fourteen patients with cancer of the prostate of the 3-4 stage were held under examination. The ages of the patients ranged from 60-79.

The presence of prostate cancer of the 3-4 stage, the necessity of orchiectomy, and a satisfactory mental and physical state served as criteria for inclusion in the study. In the aim of diagnosing prostate cancer and determining its stage all patients underwent rectal investigation of the prostate gland, transrectal ultrasound scanning and biopsy of the prostate gland, transabdominal ultrasound scanning of the bladder, kidneys and liver, radiography of the thorax, NMR of the organs of the pelvis, scintigraphy of the bones of the skeleton, and determination of the level of PSA in the serum of the blood.

Patients were excluded from the study if they had any of the following: infectious illnesses of the lower urinary paths, varicocele, prior operations on the prostate gland or bladder, changes in the function of the liver (content of transaminase and/or bilirubin higher than the norm), or a content of creatine in the serum higher than 0.11 mmol/l. Furthermore, patients who had received medical treatment in the last three months with diuretics, antiandrogens, or preparations affecting the α-adrenalin receptors, or had received treatment using finasterid or permixon were also excluded. Upon initial test no patients showed clinical signs of tumors of the CNS. Patients were excluded if in their past medical history they had trauma of the CNS, epilepsy, or other illnesses and lesions of the brain. All patients included in the study did not have hyperprolactinemia before the start of treatment, characteristic of a significant number of adenoma of the hypophysis.

An overall blood and urine analysis was done on patients before the therapy and one month into treatment. Levels of creatine, urea, common bilirubin, glucose, and the activity of alanine aminotransferase and aspartate aminotransferase were also determined before the beginning and one month into therapy.

All patients made up one group within which results of tests were compared before and one month after orchiectomy.

Hormonal research and determination of the level of PSA

To Determine the lutenizing hormone (LH) in the serum of the blood, follicle-stimulating hormone (FSH), prolactin, somatropic growth hormone (STH), testosterone, 17β-estradiol (E_2), estrone, 5α-dihydrotestosterone, insulin, 25-

$OHVitD_3$, main fibroblast growth factor (bFGF), epidermal growth factor (EGF), transforming growth factor-β (βTGF), insulin-similar growth factor-1(IGF-1), PSA, interlukin 1β (IL-1β), and tumor necrosis factor α(TNFα) an immuno-enzymal method was used. A step in this method was to draw blood in the morning, on an empty stomach, at a fixed time (08.00-10.00) (Morales A. et al., 1996; Loran O.B. et al., 1999).

While conducting the study a chemiluminescent analyser IMMULITE-2000 (DPS, США) was used as well as a many-channelled spectrophotometer ELx 800 (BIO-TEK Instruments Inc., USA).

To determine the levels of LH, FSH, prolactin, and testosterone kits made by the firm "Alkor Bio" (St. Petersburg, Russia) were used. Levels of STH and IGF-1 were determined using kits of the firm BCM Diagnostic (USA), E_2, PSA and insulin were determined using kits by the firm DPC (USA), 5α- dihydrotestosterone with a kit by the firm Alpha Diagnostic International (San-Antonio, USA), estrone with a kit by the firm DSLabs (USA), 25-$OHVitD_3$ by the firm Biomedica, Be Gesellschaft mbh (Austria), bFGF, EGF, TGF-β were determined with a kit by the firm Cytimmune Sciences Inc. (Maryland, USA), and IL-1β, TNFα with kits by the firm "Scientific Research Institute OChB "Proteinovii Contour"(St. Petersburg, Russia). The minimal concentration of E_2, which permitted a display of the method, was 73.4 pmol/l.

Normal levels of LH range from 2.2 – 9.8 IU/l (Sufi S.B. et al., 1992); FSH 1.0 – 11.8 IU/l; testosterone 13-33 nmol/l; prolactin 105-540 mIU/l; STH 0-264 pmol/l; normal levels of 5α-dihydrotestosterone range from 0.86-3.4 nmol/l (according to the figures of the makers of the test-system); 17β-estradiol in the blood plasma of men from 22-161 pmol/l (Whitley R.J. et al., 1994); normal levels of PSA 0-4.0 ng/ml; insulin 43.0-193.7 pmol/l; IGF-1 40-280 mkg/l; TGF-β 19-71 ng/ml; IL-1β 0-50 pg/ml; TNFα 0-50 pg/ml (according to the figures of the makers of the test-system).

Sensitivity and coefficients of the variations constituted, for LH- 0.5 IU/l and 8%; for FSH- 0.5 IU/l and 8%; for prolactin- 10 mIU/l and 8%; for STH- 1.3 pmol/l and 8%; for testosterone – 0.7 nmol/l and 8%; for 5α- dihydrotestosterone – 0.24 nmol/l and 11.7%; for 17β- estradiol – 0.1 pmol/l and 8%; for estrone 3.7 pmol/l and 7%; for PSA 0.01 ng/ml and 8%; for insulin – 7.2 pmol/l and 10%; for 25-$OHVitD_3$ 1.5 nmol/l and 10%; for bFGF 0.49 ng/ml and 8%; for IGF-1 0.01 mkg/l and 7%; for EGF 0.1 pg/ml and 7%; for TGF-β 0.2 pg/ml and 7.9%; IL-1β 1 pg/ml and 5%, TNFα-1 pg/ml and 5%.

Determination of the activity of acid phosphatase, alkaline phosphatase and the level of Ca^{++}

Determination of the activity of acid phosphatase, alkaline phosphatase and the level of Ca^{++} was done using the caloro-metric method on the analyzer Kon Specific (Finland) with the use of kits by the firm Randox (Great Britain). Normal indicators of acid phosphatase range from 0-5.7 E/l and for alkaline phosphatase 60-270 U/l. The normal level of Ca^{++} is 2.10-2.70 mmol/l. Sensitivity and coefficients of the variations constituted 0.33 E/l and 7.3% for acid phosphatase;

8.3 U/l and 5.9% for alkaline phosphatase. Sensitivity and coefficients of variations for Ca^{++} constituted 0.25 mmol/l and 1.8%.

Statistical analysis

The evaluation of results, received before orchiectomy and one month after the operation was done using the method of dispersion analysis of repeated measurements. Estimation of the significance of the distinctions between changes in the indicators was made on the basis of the twin Student criteria. All figures, in the text and in the tables, are represented in the form of average values and their standard deviations (M±σ). Also shown are the average values of the parameters (đ), their standard errors ($s_{đ}$) and the values of the Student criteria (t) (Glantz, 1999).

Results

In the initial test the average level of LH and FSH did not exceed normal values. The level of prolactin of all patients was within the norm. The average indicators of IL-1β, acid phosphatase, alkaline phosphatase, TNFα, and PSA were increased, but testosterone and βTGF were reduced (Tables 1, 2, 3, 4).

One month after the orchiectomy the majority of patients, despite the reduction in dysuria, noticed a loss of strength, a loss of appetite and sleep, and congestion. Upon comparison with initial data, a significant reduction of the levels of testosterone, 5α-dihydrotestosterone and 17β-estradiol was observed in all patients (on average 90.4%; 36.9% and 23.7% respectively), while an increase of LH and FSH was observed (on average 229% и 359% respectively). The reduction of testosterone was accompanied by a statistically significant increase of prolactin (on average 50.7%), STH (on average 46.6%) and of estrone (on average 69.9%). The decrease in 5α-dihydrotestosterone determined the reduction of EGF (on average 68.3%).

The decrease in the level of testosterone was accompanied by a statistically significant increase: of insulin (on average 53.7%), IGF-1 (on average 17,3%), bFGF (on average 43,9%), 25-OHVitD_3 (on average 58.9%), Ca^{++} (on average 6.5%), and decrease: of βTGF (on average 47.6%), IL-1β (v 58.7%), TNFα (on average 69.3%), acid phosphatase (on average 31.9%), alkaline phosphatase (on average 30.5%), PSA (on average 81.1%) (Tables 1, 2, 3, 4).

Discussion

The age-related reduction of testosterone, formed in patients before orchiectomy, testifies to the fact that PADAM accompanies the development of prostate cancer. A significant part of tissues have testosterone receptors and can be analyzed as targets for androgens. Testosterone takes part in the processes of growth and differentiation of cells (Lopatkin, 1998; Kettail et al., 2001). PADAM disrupts the natural cycle of development of cells containing androgen receptors.

The given changes manifest themselves by a reduction in the intensity of reproduction of cells in an entire series of tissues as a proportion of aging (Farber, 1995; Sporn, 1996; Bershtein, 2000). The transition of androgen-independent transitory-proliferation cells into the androgen-dependent pool of transforming cells (Lopatkin, 1998), which require for further development the presence of a physiologically necessary level of testosterone, is accompanied by a breach of the process of differentiation. The risk of their neoplastic transformation rises (Russo et al., 1997; Bershtein, 2000). An infringement of the development of the cells on the testosterone-dependent stage regularly hinders the development of the final stage of the cell cycle – apoptosis.

In order to make up for the inadequacy of the mytogenic action of testosterone a whole set of compensatory-adaptation reactions is formed. These reactions touch on endocrinal, paracrinal, and autocrinal levels. Distinctive contact and cross-talk of the pepti-dependent and steroid-dependent mechanisms of regulation is observed (Bershtein, 2000).

In view of the interdependence of the neurohumoral regulatory processes (Lavin, 1999) a reduction of the production of testosterone is reflected on endocrinal regulation as a whole.

The reduced level of testosterone stimulates not only the secretion of LH, but the secretion of gonadoliberin as well (Lavin, 1999) and (secondly) the secretion of FSH.

Upon the first test the level of LH and FSH in most patients, despite the low level of testosterone, did not exceed the normal values. A month after the orchiectomy, besides a reduction in the level of testosterone, 5α-dihydrotestosterone, and 17β-estradiol, all patients showed a significant increase of LH and FSH ($p<0.001$).

The increased levels of testosterone and 17β-estradiol repress the secretion of LH and FSH, as well as the secretion of gonadoliberin (Lavin, 1999). Testosterone and 5α-dihydrotestosterone connect to one and the same receptor. The ability to connect with the androgen receptor is higher for 5α-dihydrotestosterone in comparison with testosterone (Lavin, 1999). Therefore, when the level of testosterone goes down and there is a corresponding response in the increase of the level of 5α-dihydrotestosterone and 17β-estradiol in men with PADAM (Pechersky, 2002), in some men there is no increase in the level of LH and FSH.

Thus it is essential to consider the increase of the levels of 5α-dihydrotestosterone and 17β-estradiol, equally to the increase in the level of LH, FSH and the reduction of the level of testosterone when diagnosing PADAM.

After the orchiectomy an increase in the level of STH ($p<0.05$) was observed, which depends on the stimulation of somatoliberin (Lavin, 1999). An increase in the secretion of somatoliberin and repression of the secretion of somatostatin is observed during reduction of the sensitivity of the hypothalamic centers to inhibition with glucose. The given changes are found after 30-40 years. Insulin resistance promotes an increase of STH. After orchiectomy the level of insulin regularly increased ($p<0.05$). Formation of STH is additionally stimulated by

Vitamin D (Lavin, 1999; Bershtein, 2000; Kettail et al., 2001), the level of which increased after orchiectomy ($p<0.05$).

After orchiectomy the level of prolactin continually increased ($p<0.05$).

The fall in the levels of testosterone and 17β-estradiol was accompanied by an increase in the activity of the aromatase. This confirms the increase of the level of estrone ($p<0.05$). Just like 17β-estradiol, estrone is formed under the influence of aromatase (Lavin, 1999). The formation of estrone from adrenal androgen – androstendion allows one to evaluate the activity of aromatase even when the level of testosterone is significantly reduced after orchiectomy.

Seeing that when the level of testosterone is decreased the activity of aromatase as well as of 5α-reductase increases (Pechersky, 2002), the increase in activity of aromatase after orchiectomy points to the growth of 5α-reductase activity.

Thus the reason for the decrease in production of 5α-dihydrotestosterone and 17β-estradiol in patients following orchiectomy is that the level of testosterone decreases significantly (from which 5α-dihydrotestosterone and 17β-estradiol form). Despite this, the enzymatic activity, contrarily, increases.

An increase in aromatase activity may be promoted by prolactin (Pankov, 1983), IGF-1 (Mendelson et al., 1987; Ryde et al., 1992; Bershtein, 1998), insulin (Lueprasitsakul et al., 1990) and vitamin D (Jakob et al., 1995; Bershtein, 1998), the levels of which regularly rose after orchiectomy ($p<0.05$ for all three indicators).

The increase in the activity of aromatase and 5α-reductase is determined by the physiological role of estrogens and 5α-dihydrotestosterone.

Estrogens induce an intensive metogenesis in the tissues containing specific receptors (Burrows et al., 1952). The estrogen receptors are located both in the cells of the stroma and in the epithelia of the prostate gland, with a primary localization in the stroma. The stimulation of growth of stromal cells induces a proliferation of the epithelia (Lopatkin, 1998).

5α-dihydrotestosterone and testosterone, connecting with one and the same inner-cell receptor (Lavin, 1999), stimulate the proliferation activity of the cells (Zazerov et al., 1998).

The reduction of the levels and, accordingly, of the kariokynetic activity of testosterone ($p<0.005$), 5α-dihydrotestosterone ($p<0.05$) (and, accordingly, of EFR ($p<0.05$) (Zazerov et al., 1998)), and 17β-estradiol ($p<0.05$) after orciectomy is compensated not only by an increase in aromatase and 5α-reductase activity, but also by an additional exertion of production by cells of peptidial growth factors. The given changes are conditional upon the endocrinal activators of reproduction. (Vasilev, 1997; Bershtein, 2000).

In all patients after orchiectomy there ensued a reliable increase of the level of bFGF ($p<0.01$). bFGF has the most pronounced stimulating influence upon the proliferation of the epithelia. By its kariokynetic activity bFGF surpasses EFR and several other growth factors (Lopatkin, 1998).

After orchiectomy an increase in the formation of IGF-1 ($p<0.05$) was observed. This was promoted by the increase in the secretion of STH ($p<0.05$). STH and IGF-1 manifest pronounced mitogen action (Lavin, 1999).

IGF-1 and a set of other peptides carry out the role of the estromedin – to be the intermediary of the effect of estradiol. Their effect is manifested thanks to stimulation of the phosphorylation of the estrogenic receptors (Lippman et al., 1989; Bershtein, 2000).

The receptor of IGF-1 is similar to the receptor of insulin, and therefore IGF-1 can connect with the receptors of insulin and activate them(Lavin, 1999). The increase in the levels of IGF-1 ($p<0.05$) and insulin ($p<0.05$) in patients after orchiectomy is a compensatory answer to the development of insulin-resistance.

Insulin, along with IGF-1, raises the kariokynetic activity of the cells. From these positions it’s possible to examine insulin-resistance as an instrument for the increase of the level of insulin, STH, IGF-1 and, accordingly, they’re kariokynetic activity. The increase in the levels of the given indicators is characteristic of the stage of the promotion of tumor growth (Yam D. et al., 1996; Bershtein, 2000).

The increase in aromatase activity and the levels of the majority of growth factors after orchiectomy indicates that compensatory-adaptation reactions which develop when the level of testosterone goes down are directed towards an increase in the activity of the cells. Their expression is proportional to the degree of reduction of the testosterone level.

The given changes combine with the oppression of the formation of βTGF ($p<0.05$) - a factor responsible for the consequential passage by the cell stages of the stages of differentiation and the start of apoptosis. (Lopatkin, 1998; Bershtein, 2000).

The most important regulators of cell immunity are cytokines (IL-1, TNFα and others), secreted by activated macrophages, monocytes and NK- by the cells (Yarilin, 1999; Roitt et al., 2000). After orchiectomy a reliable decrease of the initially-increased levles of IL-1β($p<0.05$) and TNFα($p<0.05$) was determined.

The given changes were accompanied by a set of cytotoxic factors of cell immunity.

TNFα, hydrolases (acid phosphatase, alkaline phosphatase, serin proteinases and esterases) components of the compliment, and highly-active forms of oxygen and nitrogen determine to a significant degree the cytolytic (including anti-tumor) action of monocytes macrophages, neutrophils, and cytotoxic T cells and NK cells. After orchiectomy the initially-high levels of acid phosphatase, alkaline phosphatase and TNFα reliably decreased ($p<0.01$; $p<0.05$ and $p<0.05$).

TNFα, besides its regulatory function, possesses pronounced cytotoxicity which manifests itself in the destruction of tumorous cells. By their construction receptors of TNFα are similar to Fas, which testifies to the potential participation of TNFα (in addition to its regulatory and cytotoxitic action) in the start of the apoptosis program (Yarilin, 1999; Roitt et al., 2000).

Acid phosphatase, which posseses cytolitic activity, is held in macrophages, in primary (auzorophile) granules of neutrophiles and in several other cells of the immune system (Yarilin, 1999; Roitt et al., 2000).

Alkaline phosphatase also posseses cytolitic activity. It is held in secondary (specific) granules of neutrophiles and, equally to other highly-active substances and enzymes, is capable of causing death in tumorous cells (Yarilin, 1999).

The formation of free radicles, peroxide, and other highly-active products is accompanied by a high use of glucose. The enzymization of glucose is accompanied by the accumulation of NADPH; the interaction of the latter with a molecule of oxygen leads to the formation of superoxide-anion (O_2^-). During the resulting reactions hydrogen peroxide (H_2O_2), hydroxyl-radical (OH^-) and other products are formed (Yarilin, 1999; Roitt, 2000). The increased level of glucose, necessary for this process, is kept up owing to insulin resistance. After the orchiectomy the average value of the level of insulin reliably increased ($p<0.05$), which points to the strengthening of the given compensatory mechanism.

Cytolysis of the cells-targets of the malignant tumor leads to its incomplete necrosis (Yarilin, 1999). The given process has an autoimmune nature. The cytolitic action of the NK-cells on the freshly-formed tumorous cells is shielded by receptors which are limited by killing (KIR) (Yarilin, 1999), and therefore necrosis develops in the most early-formed divisions of the tumor.

In all patients before orchiectomy a high level of PSA was found. PSA is a serine proteinase – an enzyme, relating to the class of hydrolases. α1-antichemotripsine and α_2-macroglobulin connect with PSA, converting it into an inactive form (Loran et al., 1999; Bershtein, 2000). Besides the epithelia of the prostate gland the serine proteinases are formed by a whole set of cells.

Granules of macrophages, neutrophiles, cytotoxic T- cells and NK-cells also contain serine proteinases and esterases of the chemotripsin type. The regulation of the activity of the proteinases is done by their inhibitors, secreted by the macrophages: by α-antichemotripsin and α_2-macroglubin. Besides the manifestation of cytotoxicity serine proteinases can cause in the cells-targetsfragmentation of DNA and the start of the program of apoptosis, acting on the path of inner-cell signalization. Serine proteinases participate in the antibody-independent alternative path of activation of the compliment (Yarilin, 1999; Roitt et al., 2000).

Thus the increase of PSA, determined before orchiectomy in patients with prostate cancer, is not only the consequence of a secretion of the malignant cells of the epithelia of acinuses germinating the surrounding tissues entering into the bloodstream, but also the expression of an overall compensatory activation of the system of the complement and of cell immunity.

Ca^{++} takes part in the activation of the compliment, in the perphorin-dependent mechanism of interaction with the target cytotoxic T-cells и NK-cells, and also participates in the processes of degranulation of identification by the lectin receptors of NK-cells of antigens of the cells-targets (Yarilin, 1999; Roitt, 2000). A month after the orchiectomy the average value of the level of Ca^{++} rose ($p<0.05$).

The increased values of IL-1β, TNFα, acid phosphotase, alkaline phosphotase, PSA determined before orchiectomy and the increase in the level of calcium after orchiectomy testifies to the development of a compensatory reaction of anti-tumor cell immunity in response to the increase of proliferate activity among patients with PADAM. The given reaction is directed at the utilisation of the formation of atypical cells and the regulation of apoptosis.

The reduction of regulatory as well as of the majority of cytotoxic factors of cell immunity, testifies to the decompensation of mechanisms of anti-tumor immunity in patients after orchiectomy.

Thus the reduction of the level of testosterone causes an increase in kariokynetic activity, the breach of the regulation of the cell-cycle and the start of apoptosis, and (when the reduction of the level is significant) the decomposition of antitumor immunity. The given changes create the conditions for the development of a new tumor from low-differentiated androgen-independent epithelial cells, despite the dystrophic changes happening in the androgen-dependent cancer cells of the original tumor.

Taking into account the many-staged oncogenesis (Kopnin, 2000; Bershtein, 2000) and the good, quick effect, it's possible to expect the androgen blockade to be very promising under the condition that it will be done in relatively short cycles, and that upon completion of the therapy that the hormonal balance will be reduced. It's not possible to restore the chemical balance without the production of testosterone by the patient's own Leydig cells (Pechersky, 2002). For this reason only a pharmacological androgen blockade can be considered effective (in view of its reversibility).

Table 1. Levels of LH, FSH, prolactin, and STH before and one month after orchiectomy.

	LH	FSH	Prolactin	STH
μ ± σ before	7.2 ± 8.8	8.3 ± 11.8	219.7 ± 100.1	132.0 ± 189.2
μ ± σ after	23.7± 14.1	38.1 ± 17.8	331.3 ± 220.4	193.6 ± 268.4
đ	16.5	29.8	111.6	61.6
$s_đ$	3.4	3.9	49.5	26.4
t	4.907	7.678	2.253	2.450
	p<0.001	p<0.001	p<0.05	p<0.05

N=14

Таблица 2. The levels of testosterone, DHT, E_2, estrone and PSA before and one month after orchiectomy.

	Testosterone	DHT	E_2	Estrone	PSA
μ ± σ before	11.4 ± 8.9	2.333± 1.707	99.6 ± 36.8	2921.0 ± 3505.7	69.3 ± 59.3
μ ± σ after	1.1 ± 0.7	1.472± 0.918	76.0 ± 8.0	4966.0 ± 6249.2	13.1 ± 22.5
đ	-10.3	-0.861	-23.6	2044.6	-56.2
$s_đ$	2.5	0.364	10.3	887.9	15.3
t	4.150	2.367	2.287	2.303	3.671
	p<0.005	p<0.05	p<0.05	p<0.05	p<0.005

N=14

Таблица 3. The levels of insulin, bFGF, EGF, IGF-1 и βTGF before and one month after orchiectomy.

	Insulin	bFGF	EGF	IGF-1	βTGF
μ ± σ before	58.8±22.2	26.9±10.0	339.2±199.9	184.0±76.9	1748.5±1271.4
μ ± σ after	90.4±53.8	38.7±14.4	107.6±154.2	215.9± 66.3	916.9± 664.3
đ	31.6	11.8	-231.6	31.9	-831.6
$s_đ$	12.2	3.5	104.7	12.8	366.8
t	2.531	3.356	2.213	2.489	2.267
	p<0.05	p<0.01	p<0.05	p<0.05	p<0.05

N=14

Table 4. Levels of $25OHD_3$, IL-1β, TNFα, Acid phosphatase, Alkaline Phosphatase and Ca^{++} before and one month after orchiectomy.

	25-ONVitD	IL-1β	FNO-α	Acid Phosphate	Alkaline Phosphate	Ca^{++}
μ ± σ before	43.2 ± 34.7	227.9 ± 216.3	75.5 ± 81.3	7.2 ± 3.7	548.8 ± 592.9	2.3 ± 0.1
μ ± σ after	68.7 ± 95.5	94.1 ± 134.4	23.2 ± 12.0	4.9 ± 2.2	381.3 ± 439.2	2.5 ± 0.3
đ	25.5	-133. 8	-52.3	-2.3	-167.5	0.1
$s_đ$	11.7	57.2	20.6	0.7	57.0	0.07
t	2.168	2.340	2.537	3.183	2.939	2.273
	p<0.05	p<0.05	p<0.05	p<0.01	p<0.05	p<0.05

N=14

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