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Disturbed homeostasis of zinc and other essential elements in the prostate gland dependent on the character of pathological lesions

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Abstract Pathophysiological changes in the prostate take the form of benign prostate hyperplasia (BPH) and prostate adenocarcinoma (PCa). In prostate, zinc is particularly important to its normal functioning, especially in terms of the consequences of hormone disturbance. The aim of this study was to assess the levels of Zn, Cu, Ca, Mg, and Se in the prostate dependent on the character of patological changes. Zinc, copper, magnesium and calcium were determined by AAS and selenium with spectrofluorometric method. Zn levels in BPH patients were over twofold higher than in controls. On the other hand, in the patients with PCa, the levels of Zn were found almost three times lower than in BPH patients and by almost 50% lower than in controls. In this study, significant changes in the levels of other essential elements were observed. The results apparently confirm the disturbed homeostasis of zinc and other essential elements in the etiology of BPH and PCa.

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Introduction

Pathophysiological changes in the prostate gland usually take the form of benign prostate hyperplasia (BPH) and prostate adenocarcinoma (PCa) (Guess 2001). The human prostate gland is a complex organ comprised of differing ontological, morphological and functional components defined as the peripheral zone (about 70%), central zone (about 25%), transition zone (2–5%), and periurethral region (Kumar 2007).

On account of the location (BHP most frequently embraces the transition and/or central zone of the prostate, while PCa usually arises in its peripheral zone) and the type of tissue texture, it is thought that the etiology of these two kinds of changes differs, however, the hormone theory dominates in both cases (Alcaraz et al. 2009; Erbersdobler et al. 2004).

Although the majority of studies provide explicit evidence that the etiology of BHP (most probably resulting from andropause, a condition observed in all men) differs from that of PCa (of which etiology is still ambiguous), the assumption that the hormonal disorder of androgens (testosterone in particular) and estrogens is most likely a causative agent responsible

for these two pathologies appears to be irrefutable. The hormone theory is based on the well known hormone-sensitivity of the prostate gland as the environment of its localization is strongly dependent on the hypothalamus-pituitary-testes axis (Schatzl et al. 2001).

One of the fundamental functions of the prostate gland is the metabolism of testosterone, resulting among others in the production of biologically active dihydrotestosterone (DHT), a critical growth mediator of prostate cells, their proliferation and secretory activities (Carson and Rittmaster 2003). It is also important for the normal homeostasis of the prostate gland that it remains under the influence of two estrogens produced in very small quantities, estron and 17-beta-estradiol (Calle and Kaaks 2004).

In men aged over 30, the levels of androgens, especially testosterone, already begins to gradually decrease (andropause). The decline in the testosterone level is a resultant of several overlapping processes, including aging with the retained hormonopoiesis of nuclei, which is one of the crucial process. Mutual hormone relationships are regulated on the basis of negative feed-back, therefore, the lower level of testosterone triggers a cascade of changes in the hypothalamus-pituitary-testes axis, resulting in its enhanced synthesis . The consequences of the aforesaid processes may include the disturbed balance of hormones in general, and the disturbed metabolism of testosterone in particular, leading finally to uncontrolled hyperplasia of the prostate gland (Buschemeyer and Freedland 2007).

Still more attention is being paid to the role played by the homeostasis of essential elements for preserving the normal function of all human organs. As regards prostate, zinc (Zn) appears to be an element that is particularly important to its normal functioning, especially in terms of the consequences of hormone disturbance. Therefore, it seems that the highest Zn levels (calculated per 1 g wet tissue) found just in the prostate gland cannot be regarded as pure chance. This indicates that Zn must play here a very important role. The prostate is known to accumulate high levels of zinc, but levels are markedly decreased with cancer development. Yan et al. (2008) hypothesized that zinc plays a critical role in maintaining DNA integrity in the prostate and zinc deficiency would lead to increased DNA damage and altered DNA damage response mechanisms.

Although Zn implication in the prostate functioning has not yet been explicitly linked with a number of hormonal and biochemical changes, which occur in this organ, it has already been indicated that this element is one of the major mediators of testosterone metabolism Salgueiro et al. 2004. Studies performed on both laboratory animals and prostate cell lines have evidenced that Zn is an inhibitor of two key enzymes involved in the process of testosterone metabolism, 5α-reductase [EC.1.3.99.5] (converts testosterone to DHT) and aromatase [EC1.14.14.1] (catalyzes estrogen production). Zn is also essential for the regular Kreb cycle in the prostate gland, where it plays the role of an inhibitor of m-aconitase [EC 4.2.1.33] that transforms citrate into isocitrate (Costello and Franklin 2009; Costello et al. 2005).

Numerous in vitro and in vivo studies have evidenced that Zn performs another equally important function in the prostate gland—it induces apoptosis in this organ. An appropriately high Zn level is thus essential for retaining the balance between proliferation of prostatic cells and their physiological death (Costello et al. 2005; Franklin and Costello 2007; Feng et al. 2003).

The disturbed homeostasis of other essential elements besides zinc, especially of copper (Cu), calcium (Ca), magnesium (Mg) and selenium (Se) can also play a very important role in the mechanism of uncontrolled cellular hyperplasia.

It has been demonstrated that the disturbed homeostasis of Cu plays an essential role in cancer angiogenesis, especially in the initiation of this process. Cu mediates the "involvement" of cellular proliferation via the activation of angiogenic growth factors (Majumder et al. 2009). Cu implication in the carcinogenic process, may be also linked with its ability to bind to some proteins and thus to acquire the angiogenic activity. This explains a many fold increase in Cu levels in serum and cancer-affected tissues in different malignancies (Jain et al. 1994; Uauy et al. 1998).

All cells to grow and divide need ions of other elements, e.g., Ca and Mg. It is well known that mammalian cells are exceptionally sensitive to Ca deficiency in two phases of the cellular cycle, in early G1 phase and at the turn of G1/S phases (Wolf et al 2007). On the other hand, changes in Mg levels in cells may induce a number of pathological lesions. Magnesium among its other functions stabilizes

cellular membranes, and its insufficient supply enhances the permeability of cell membranes and sensitivity to oxygen free radicals, leading to the generation of numerous cellular abnormalities (Wolf et al 2007; Quintero et al. 2006).

Selenium is another element that due to its anti-tumor effects appears to play a crucial role in the etiology of carcinogenic process. Many in vivo and in vitro studies have provided compelling evidence that Se compounds inhibit carcinogenesis (Tapiero et al. 2003; Sarafanov et al. 2008).

The aim of this study was to assess the levels of Zn and other essential elements (Cu, Ca, Mg, and Se) in the prostate gland dependent on the character of the changes (BPH and PCa). It was also attempted to explain the role of Zn in the etiology of BPH and PCa.

Materials and Methods

Zinc, selenium and other essential elements were determined in 67 prostate tissue specimens, of which 27 showed hyperplasia (*Hyperplasia prostate*) and 29 adenocarcinoma (*Adenocarcinoma prostate*). *Post mortem* derived tissues (11), free of histopathologic changes characteristic of PCa or BPH were used as controls. Intra-surgery and transurethral electroresection (TURP) specimens of malignant tissues (BPH and PCa) were derived from the patients of the Maria Skłodowska-Curie Urological Hospital in Zgierz.

In individual control and study groups, the patients' age (years) fell into the following age groups: controls, 49–67 years; BPH patients, 55–76 years; and PCa patients. 53–81 years.

Specimens of tissues with benign prostate hyperplasia were obtained from the transitional zone and those with prostate adenocarcinoma from the peripheral zone of the prostate gland. The control specimens (*post mortem*) were derived through a transverse cross section of the whole organ.

Prior to the analysis, all tissues were pathomorphologically assessed to confirm the diagnosis.

Zinc, copper, magnesium and calcium were determined after mineralization by flame atomic absorption spectrometry (GBC Avanta PM). Selenium was determined with spectrofluorometric method after mineralization and extraction with cyclohexane (HITACHI F-4500).

The intralaboratory quality control of determinations based on the certified standard lyophilized bovine liver SRM 1577b (National Institute of Standards and Technology, Gaithersburg, USA) contained certified concentrations of the following elements [μg/g]: Zn (127 ± 16), Cu (160 ± 8), Ca (116 ± 4), Mg (601 ± 28), Se (0.73 ± 0.06). Mean discrepancies of the obtained results compared with certified values expressed as RSD were: Zn ± 0.3; Cu ± 8.3; Ca ± 6.3; Mg ± 6.9 and Se ± 3.5%.

The study was approved by the Ethics Committee for Scientific Research at the Medical University of Lodz.

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Results

The levels of Zn and other essential elements (Se, Cu, Ca, and Mg) determined in tissue specimens of controls and patients with diagnosed BPH and PCa are given in Figs 1, 2, 3, 4, 5.

As depicted by the figures, the analysis of element determinations in prostate tissues not affected by hyperplastic lesions (controls) clearly shows that Ca, Mg and Zn form the group of elements with the highest concentrations (μg/g wet tissue) in these tissues.

In tissues of patients with diagnosed BPH, a significant increase in the concentration of all determined elements was found as compared to controls,

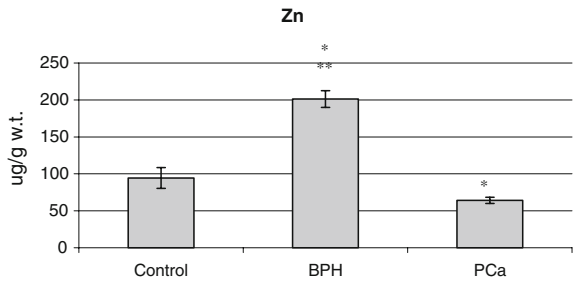

Fig. 1 Zinc (Zn) concentrations (μg/g wet tissue) in histopathologically unchanged prostate tissues (controls) and in tissues affected by benign prostate hyperplasia (*BPH*) and prostate adenocarcinoma (PCa). All values are expressed as means ± SEM (* Results statistically significant compared to controls, confidence interval (CI):95%; ** Results statistically significant compared to PCa, CI:98%)

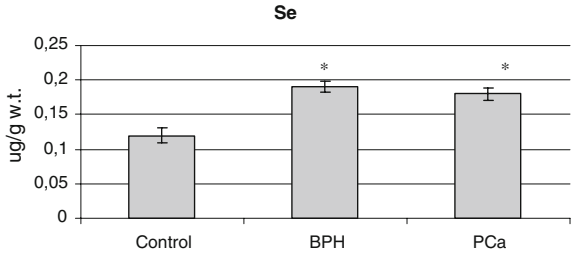

Fig. 2 Selenium (Se) concentrations (μg/g wet tissue) in histopathologically unchanged prostate tissues (controls) and in tissues affected by benign prostate hyperplasia (*BPH*) and adenocarcinoma (PCa). All values are expressed as means ± SEM (* Results statistically significant compared to controls, CI:95%)

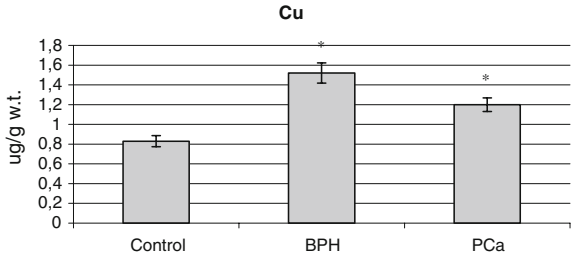

Fig. 3 Copper (Cu) concentrations (μg/g wet tissue) in histopathologically unchanged prostate tissues (controls) and in tissues affected by benign prostate hyperplasia (*BPH*) and prostate adenocarcinoma (PCa). All values are expressed as means ± SEM (* Results statistically significant compared to controls, CI:95%)

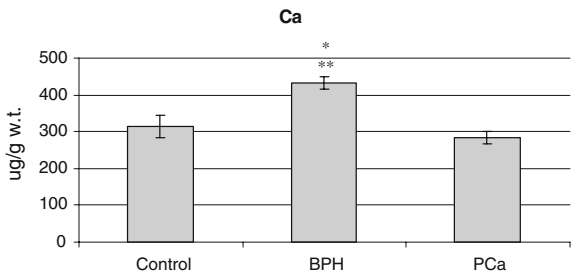

Fig. 4 Calcium (Ca) concentrations (μg/g wet tissue) in histopathologically unchanged prostate tissues (controls) and in tissues affected by benign prostate hyperplasia (*BPH*) and prostate adenocarcinoma (PCa). All values are expressed as means ± SEM (* Results statistically significant compared to controls, CI:95%; ** Results statistically significant compared to PCa, CI:98%)

but the highest increase was observed for Zn (over twofold) (Fig. 1) and Cu (about 1.8-fold) (Fig. 2).

Almost entirely opposite effect was found in PCa-affected prostate tissues. The majority of elements

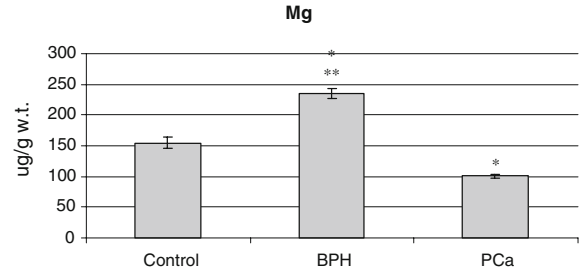

Fig. 5 Magnesium (Mg) concentration (μg/g wet tissue) in histopathologically unchanged prostate tissues (controls) and in tissues affected by benign prostate hyperplasia (*BPH*) and prostate adenocarcinoma (PCa). All values are expressed as means ± SEM (* Results statistically significant compared to controls, CI:95%; ** Results statistically significant compared to PCa, CI:98%)

(except for Se and Cu) showed significantly lower levels, especially as compared to the BPH group. The most spectacular decrease was observed for Zn compared to the BPH (over threefold) and the control (almost 1.5-fold) groups (Fig. 1). A similar tendency was observed for Ca and Mg (Figs. 4, 5). Only Cu level in the PCa-affected tissues was significantly higher and comparable to that found in BPH tissues (Fig. 2).

Quite different tendency was observed for selenium. Its levels were significantly higher in both BPH and PCa groups than in controls (Fig. 3). Moreover, its levels in both types of pathological tissues (PCa and BPH) were almost identical.

To better visualize the observed changes in the levels of individual elements in the three groups of tissue specimens (BPH, PCa and controls), their mole ratios are also given (Table 1).

As shown in Table 1, the most visible changes found in this study concerned the Cu and Se ratio to Zn. In the histopathologically unchanged tissue the

Table 1 Mean mole ratios between elements under study in prostate tissue specimens of the control, benign prostate hyperplasia (BPH), and prostate adenocarcinoma (PCa) groups

	Controls	BPH	Pca
Cu/Zn	1/111	1/130	1/53
Se/Zn	1/970	1/1290	1/440
Mg/Zn	1/4.4	1/3.2	1/4.2
Ca/Zn	1/5.4	1/3.5	1/7.0
Se/Cu	1/8.7	1/10.0	1/8.2
Mg/Ca	1/1.2	1/1.0	1/1.7

Cu/Zn mole ratio was 1/111; in BPH tissue 1/130, and in PCa tissue this value decreased to 1/53 (over twofold). Despite differences in absolute values, almost identical tendency (increase in BPH and decrease in PCa) was demonstrated in the Se/Zn ratio (1/970; 1/1290; and 1/440, respectively). An opposite tendency (significant decrease in BPH and increase in PCa) was found while analyzing the mole ratio between Ca and Zn. In the group of patients with diagnosed PCa, the ratio between these elements almost doubled, especially when compared to the BPH group.

To find out and confirm the presence of disturbed homeostasis between Zn and Cu, the values of their concentrations were additionally analyzed in terms of mutual correlations in each group (controls, BPH, and PCa) (Fig. 6).

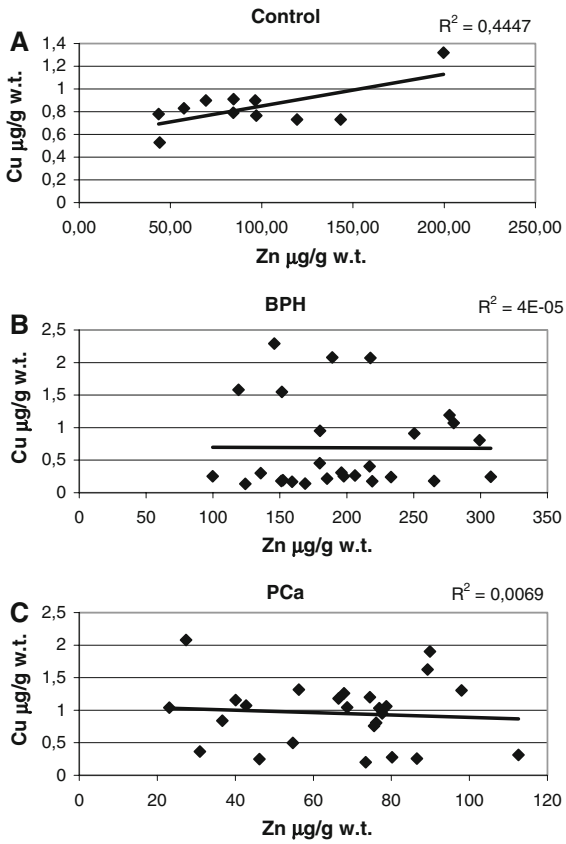

Fig. 6 Correlation between Zn and Cu in: **a** the prostate tissue histopathologically unchanged (controls); **b** the prostate tissue with benign hyperplasia (*BPH*), and **c** the tissue with adenocarcinoma (PCa)

As depicted by Fig. 6, a relatively high correlation ($R^2 = 0.44$) was obtained only for histopathologically unchanged tissues (controls) (Fig. 6a), whereas its almost complete lack was observed in the BPH tissue (Fig. 6b). Rather surprising result was yielded by the analysis of the tissue specimens with diagnosed PCa as it shows the tendency in changes at low correlation ($R^2 = 0.0069$) opposite to that observed in controls (Fig. 6c).

Discussion

The character of the lesions (BPH and PCa), which may arise in the prostate gland can be, besides the disturbed hormone balance, influenced by the diversified structure of the prostate gland not only in histological but also in biochemical terms (the Kreb cycle, testosterone metabolism). The peripheral zone is responsible for the major functions, namely the production and secretion of enormously high levels (five to tenfold higher than those found in other prostate zones) of zinc and citrate (Costello and Franklin 2006). The accumulation of high cytosolic and mitochondrial levels of Zn in normal prostate secretory epithelial cells inhibits m-aconitase, which limits the oxidation of citrate and permits net citrate production and also inhibits terminal oxidation and respiration. In malignant cells, the lost ability to accumulate high Zn levels eliminates its inhibitory effect on m-aconitase and terminal oxidation, which permits the oxidation of citrate via a functional Kreb cycle with increased production of ATP. In addition, the accumulation of high Zn levels induces mitochondrial apoptogenesis that inhibits cell proliferation. This mitochondrial apoptogenic effect is eliminated in malignant cells, which permits their proliferation (Costello and Franklin 2000).

Although BPH is clinically diagnosed in the majority of men aged about 60, this condition is initiated by the process of andropause that begins already at the age of 30–40, while PCa usually develops in elderly men. This observation is apparently essential for the etiology of the lesions of the prostate gland. Taking account of the localization of BPH and PCa in the prostate and the time of their independent development, it seems that BPH generally develops earlier. This gives rise to the question why BPH develops in the transitional zone poorly

supplied with Zn and PCa arises in the peripheral zone with the highest physiological concentration of this element.

Assuming that BPH mostly results from the disturbed metabolism of testosterone (andropause) due to the overproduction of DHT and estrogens, its development in the transitional zone with low concentration of zinc (inhibitor of testosterone conversion to DHT and estrogens) appears to be hypothetically justified. Therefore, a hypothesis that the demand for zinc in this prostate zone initiates its transfer from the peripheral zone is quite likely. Since BPH is a long (frequently taking even 20 years) progression process in the human body, it cannot be rule out that Zn transfer results in its deficiency, as well as in the deficiency of transport proteins [mainly metallothionein (MT)] in the peripheral zone. The studies carried out by (Suzuki et al. 1992) have shown a four to fivefold increase in the levels of Zn and MT (a major receptor/donor of Zn in cells) in men with diagnosed BPH, compared to the same tissue not yet affected by histopathological changes. An opposite effect was observed in patients with the diagnosed PCa, located in the peripheral zone, namely the levels of both Zn and MT were several times lower than in the control and BPH groups. Interestingly, MT gene expression in the prostate gland in patients with BPH (in the transitional zone) was found to be significantly higher than in controls (tissues derived from the transitional zone of the prostate gland with no hyperplastic features), whereas in patients with the diagnosed PCa in the peripheral zone, it was virtually undetectable. Zinc restoration leads to the re-establishment of Zn cellular homeostasis through up-regulation of MT gene expression, which may eventually result in resuming the critical selection for proliferation or death of the cell. The results obtained by Wei et al. (2008) suggest MT as a candidate tumor marker for diagnosis, prognosis and management guidance; and warrant further investigation of zinc as a potential supplement to benefit the BPH and prostate cancer treatment.

Hypothetic consequences of the lowered Zn level in the prostate peripheral zone may be a serious impairment of the Kreb cycle in this prostate zone. In their numerous studies, Costello et al. (2005) have demonstrated that a sufficiently high level of Zn^{2+} in the mitochondria of prostatic epithelial cells is indispensable to maintain appropriate levels of citrates and normal balance of energy in the prostate gland (normal prostate cells yield 14 ATP during each rotation of the Kreb cycle). They have also evidenced in in vivo studies performed on rats and in in vitro studies performed on malignant cell lines of the prostate gland that deficiency of Zn^{2+} ions in the mitochondria leads to essential oxidative disorders caused by the excessive oxidation of citrate. Zn^{2+} deficiency results in the yield of 38 ATP, which finally leads to the impairment of oxidative phosphorylation and resultant uncontrolled consequences for the cell (Costello et al. 2005).

Zn deficiency may alter the metabolism of testosterone. It is also known that Zn deficiency leads for example to a significantly enhanced activity of aromatase, resulting finally in a substantial increase in the production of estrogens, including 17β-estradiol. The higher estrogen levels may in turn increase the number of androgenic receptors and cause a substantial inhibition of apoptosis (Taylor et al. 2006). It is most likely that the altered metabolism of testosterone due to Zn deficiency in the peripheral zone may result in the overproduction of both DHT and estradiol regarded by numerous authors as a factor responsible for triggering the uncontrolled proliferation of prostate cells. Friedman's theoretical model describes the mechanism of the potential carcinogenic process in the prostate gland induced by the increased levels of DHT and estradiol (Friedman 2005; Arnold et al. 2007).

The results of this study explicitly confirmed that Zn levels in BPH patients were over twofold higher than in controls. On the other hand, in the patients with the diagnosed PCa, the levels of this element were found almost three times lower than in BPH patients and by almost fifty percent lower than in controls. Such a tendency in changes of prostate Zn levels dependent on the character of changes (BPH or PCa) has been confirmed by a quite large number of authors, except for Yaman et al. (2005) who have shown a completely opposite effect, i.e., higher Zn levels in malignant than in BPH tissues. The majority of researchers determined only Zn levels in the prostate gland without taking account of the disturbed homeostasis of other essential elements and its possible consequences for the cell. This mostly applies to copper whose metabolism is closely related to zinc.

Already discussed changes in Zn/Cu mole ratios relative to those calculated analogically in the tissue

not affected by histopathological changes or with BPH seem to confirm the essential role of Zn and Cu in the etiology of prostate cancer.

The literature data indicate that during the process of cancer development, Cu metabolism undergoes a substantial alteration. Numerous reports show the positive correlation between serum Cu concentration and the cancer incidence, tumor size, malignancy or frequency of recurrence. Such an effect has been evidenced in Hodgkin's disease, sarcomas, head and neck cancer as well as in breast, liver, lung and brain cancers (Daniel et al. 2005). The distribution of copper in malignant cells is also altered. In normal cells, Cu is localized in the cytosol, whereas in tumor cells it is found in the perinuclear region (Fuchs and de Lustig 1989).

Owing to the fact that serum Cu concentration had been controlled over many years it was possible to establish that its long-term unchanged concentration can be regarded as the positive prognosis, while its increased concentration may signify the recurrence of carcinogenic process (Voelker 2000).

The overproduction of estrogens (e.g., 17β-estradiol) is one of the factors, which determines the increase in serum Cu level, although this mechanism has not yet been elucidated. Bearing in mind that the hormone imbalance, manifested by an abnormal ratio of testosterone to overproduced estradiol (most likely a direct inducer of prostate cell proliferation), is crucial in the etiology of the lesions, it may be expected that in PCa patients the concentration of copper can be significantly increased. This has been confirmed by our studies, which also revealed a substantial increase in the concentration of this element in patients compared to controls, regardless of the character of the lesions (PBH or PCa). It appears, however, that the mechanism by which these changes occur differs in these two cases. Like in the case of Zn, the increase in Cu levels, observed in BPH, is most likely caused by the transportation of copper along with metallothionein (a common protein that transports and stores both elements) from the peripheral zone, whereas in malignant cells it probably results from the increased level of estradiol.

In this study, significant changes in the levels of other essential elements, Ca, Mg and Se were observed besides the disturbed homeostastis of zinc and copper in PBH and PCa patients.

Our analysis of Ca and Mg concentrations in the tissues under study showed that the levels of both elements were significantly higher in BPH patients than in controls (by about, 53% for Mg and about 37% for Ca). On the other hand, in PCa patients, substantial changes were revealed only for magnesium, and its levels were considerably lower in the BPH (by 60%) and control (by about 35%) groups. Although the role of magnesium in the carcinogenic process has not yet been explicitly clarified, it is thought that its lowered concentrations in PCa-affected tissues may be very dangerous to cellular stability. It is known that Mg low concentration may be responsible for the damage and instability of the DNA, leading to the helise splitting (Wolf et al. 2007; Anastassopoulou and Theophanides 2002).

In our study, calcium like magnesium showed a similarly downward albeit insignificant tendency in PCa patients. However, an opposite tendency was found in BPH tissues, which showed significantly higher Ca levels than those observed in controls, which may point out to the mechanism linked with the disturbed hormonal balance in the whole body due to the condition of andropause.

In view of the fact that the review of the literature data concerning calcium determinations in different types of human cancers has not allowed to identify any explicit direction of changes in its levels it is difficult to explain the mechanism of changes occurring in Ca levels in hyperplastic diseases. While a significant increase in Ca level has been found in the breast cancer tissue (Seltzer et al. 1970; Drake and Sky-Peck 1989), an opposite observation has been made in colon cancer (Ranade and Panday 1984).

Over the recent years, still more attention has been paid to the preventive role of selenium, especially in view of its anti-tumor potential. Therefore, Se as another essential element was determined in our study. The results showed that in tissues of both PBH and PCa patients, Se levels were significantly higher (by almost 60%) than in controls. The interpretation of the obtained results is not easy, but it may be assumed that the observed increase in Se concentration in both groups of tissues (BPH and PCa) suggests its protective role played in this organ. It may be thus taken for granted that the body "defending" itself against proliferating changes, cumulates Se, a well known anti-tumor agent. This function of selenium

has already been very well documented in numerous publications (Behne et al. 1996; Griffin 1982; Salonen 1986; Ghanter and Lawrence 1997).

It is believed that active oxygen forms produced as a result of the glutathione oxidation reaction are implicated in the mechanism of Se anti-tumor effect (Spallholz 1994). There is compelling evidence that Se administration to laboratory animals inhibited the development of the skin, mammary, pancreas, liver, colon, and lung cancers (Ronai et al. 1995). It has also been evidenced that Se inhibits the growth of various types of malignant tissues either induced or transplanted in vitro and in vivo (Willis and Wians 2003; Gray et al. 2005; Caffrey and Frenkel 1992; El Bayoumy 1994; Ip and Lisk 1994; Nano et al. 1990). Those studies showed that Se inhibits both the initiation phase of carcinogenesis and the development of cancer (Willis and Wians 2003). There are speculations over possible Se properties, which may inhibit the DNA synthesis or intensify cellular immunological response in malignant tissues (Waters et al. 2005; Ip and Lisk 1994).

The results of our studies apparently confirm the disturbed homeostasis of zinc and other essential elements in the etiology of prostatic hyperplasia (BPH and PCa). Assuming that the role of zinc in preserving the prostate hormonal balance is undisputable, it might be advisable to consider, as a preventive measure, Zn and Se supplementation in men already in the onset of andropause, the period when major hormonal changes do occur.

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