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Levels of 43 Trace Elements in Hyperplastic Human Prostate

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of this exploratory study was to clarify the differences between the prostatic levels of trace elements in patients with benign prostatic hyperplasia (BPH) and healthy male inhabitants.
Methodology: We prospectively evaluated the prostatic levels of 43 trace elements in 32 patients with BPH and 32 healthy males. Measurements were performed using instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides combined with inductively coupled plasma mass spectrometry.
Results: In the hyperplastic prostates a significant increase in the mean level of Bi, Cr, Hg, Sb, and Se and a significant decrease in the mean level of Ce, Cs, Dy, Er, Gd, Ho, La, Mo, Nd, Pb, Pr, Sm, Sn, Tb, Tm, U, and Y was observed. It was not found any differences in the mean prostatic level of Ag, Al, Au, B, Be, Br, Cd, Co, Fe, Li, Mn, Nb, Ni, Rb, Sc, Th, Ti, Tl, Yb, Zn, and Zr between BPH-patients and healthy males.
Conclusion: Present study finding of trace element contents and correlation between pairs of trace element mass fractions indicates that there is a great disturbance of prostatic trace element metabolism in BPH gland. Obtained data did not confirm a critical role of Cd and Pb accumulation in the pathogenesis of BPH. A potential age-related Zn, Fe, and Se deficiency in the prostate has not been found as being involved in the etiology of BPH. This work data cast doubts on a beneficial

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effect of the Zn, Fe, and Se supplementations on BPH prevention and treatment. Additional studies of other chemical elements in BPH are planned.

Keywords: Prostate; benign prostatic hyperplasia; prostatic trace element contents, trace element supplementations.

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) represents the most common age-related urologic disease. Prostatic parenchyma contains two basic components: A glandular component composed of secretory ducts and acini, and a stromal component composed primarily of collagen and smooth muscle. BPH is histologically defined as an unregulated proliferation of glandular epithelium, connective tissue, and smooth muscle [1]. The prevalence of histological BPH is found in approximately 50-60% of males age 40-50, in over 70% at 60 years old and in greater than 90% of men over 70 [2]. To date, there is no precise knowledge of the cellular and biochemical processes underlying the etiology and pathogenesis of BPH [3]. There are a few hypotheses on the subject but the most common concept is based on the differentiating and growth-promoting actions of androgens [4].

In previous studies it was shown that the levels of zinc and some other trace elements in prostate are the androgen-dependent parameters and play an important role in prostate functions [5-10]. Moreover, it is well known that zinc and many other trace elements play important roles in cell proliferation, differentiation, and transformation and are essential for the regulation of DNA synthesis, mitosis and apoptosis [11]. Due to lifestyle, eating and dietary habits, and physiological effects of aging, the elderly male population is normally predisposed to conditions of trace elements deficiency [12], which can increase this population's susceptibility to BPH [13]. According to the proponents of dietary supplemental trace element usage, in the absence of such supplements, cellular trace element uptake will be depressed and trace element levels in prostate will be reduced [13,14].

On the other hand, in previous studies it was found a significant tendency for an increase in level of bismuth, cadmium, chromium, mercury, thorium, uranium, and some other potentially harmful trace elements in intact nonhyperplastic prostate from age 21 years to the sixth decade [15-17]. Moreover, it has been showed the association of cadmium, chromium, lead, and some other trace metals to BPH development and progression [18].

The trace element contents in the hyperplastic prostate have been studied, producing contradictory results [19-31]. The majority of these data are based on measurements of processed prostate samples and in many studies prostate samples are ashed before analysis. In other cases, prostate samples are treated with solvents (distilled water, ethanol etc) and then are dried at a high temperature for many hours. There is evidence that certain quantities of trace elements are lost as a result of such treatment [32-34]. Moreover, only a few of these studies employed quality control using certified reference materials for determination of the trace element mass fractions. Thus, the questions about the differences between trace element contents in intact normal and hyperplastic prostate remained open.

This work had five aims. The first was to assess the trace element mass fractions in the hyperplastic prostate using nondestructive instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides (INAA-LLR) combined with inductively coupled plasma mass spectrometry (ICP-MS). The second aim was to find differences between the results for the hyperplastic prostate and the levels of trace elements in the nonhyperplastic prostate gland of age-matched health subjects, who had died suddenly. The third aim was to compare the results obtained in this work with data from the literature. The fourth aim was to estimate the effect of age on the trace element mass fractions in the hyperplastic prostate. The final aim was to estimate the inter-correlations between trace element mass fractions in hyperplastic prostate and to compare these results with data for nonhyperplastic gland. All studies were approved by the Ethical Committee of the Medical Radiological Research Center, Obninsk. Ethics clearance is in the journals number 12 (10.12.2010).

2. MATERIALS AND METHODS

All patients studied (n=32) were hospitalized and operated in the Urological Department of the Medical Radiological Research Centre. In all cases the diagnosis of BPH has been confirmed by clinical and histological results obtained during studies of biopsy and resected materials. Before biopsy or resection a blood transfusion in the hospitalized patients was not used. None of the patients were taking a trace element supplement known to affect prostate chemical element contents. The age of patients with BPH ranged from 56 to 78 years, the mean being 65±6 years (M±SD). Using a titanium scalpel resected materials were divided into two portions to permit morphological study of prostatic parenchyma and to estimate their trace element contents.

Intact prostates were removed at necropsy from 32 men (mean age 60±11 years, range 44–87) who had died suddenly (control group). The majority of deaths were due to trauma. The available clinical data were reviewed for each subject. None of the subjects had a history of an intersex condition, endocrine disorder, neoplasm or other chronic disease that could affect the normal development of the prostate. None of the subjects were receiving medications known to affect prostate morphology or chemical element content. All prostate glands were collected within 2 days of death and divided (with an anterior-posterior cross-section) into two portions using a titanium scalpel. One tissue portion was reviewed by an anatomical pathologist while the other was used for the trace element content determination. A histological examination was used to control the age norm conformity as well as to confirm the absence of any microadenomatosis and/or latent cancer.

After the samples intended for trace element analysis were weighed, they were freeze-dried and homogenized. The pounded samples weighing about 50 mg and 100 mg were used for trace element measurement by INAA-LLR and ICP-MS, respectively. Information detailing with the INAA-LLR and ICP-MS methods and other details of the analysis was presented in our previous publication [15,17].

For quality control, ten subsamples of the certified reference materials IAEA H-4 Animal muscle from the International Atomic Energy Agency (IAEA), and also five sub-samples INCT-SBF-4 Soya Bean Flour, INCT-TL-1 Tea Leaves and INCT-MPH-2 Mixed Polish Herbs from the Institute of Nuclear Chemistry and Technology (INCT, Warsaw, Poland) were analyzed simultaneously with the investigated prostate samples. All samples of CRM were treated in the same way as the prostate samples. Detailed results of this quality assurance program were presented in earlier publications [15,17].

A dedicated computer program for INAA mode optimization was used [35]. Mean values of trace element mass fractions were taken into account in final calculation for elements measured by both INAA-LLR and ICP-MS methods. Using Microsoft Office Excel software the arithmetic mean, standard deviation, and standard error of mean was calculated for chemical element mass fractions. The reliability of difference in the results between nonhyperplastic and hyperplastic prostate glands was evaluated by the parametric Student's *t*-test and values of $p<0.05$ were considered to be statistically significant. For the estimation of the Pearson correlation coefficient between different pairs of the chemical element mass fractions in the normal and hyperplastic prostate the Microsoft Office Excel software was also used.

3. RESULTS

Arithmetic mean (M) and standard error of mean (SEM) for determined trace element mass fractions in hyperplastic (group of patients with BPH) and nonhyperplastic (age-matched control group) prostate are presented in Table 1. Table 1 also depicts the ratios of means and the reliability of difference between mean values of trace element mass fractions in BPH and normal prostate.

The comparison of this work results with other published information for Ag, Al, Au, B, Be, Bi, Br, Cd, Ce, Co, Cr, Cs, Dy, Er, Fe, Gd, Hg, Ho, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Sn, Tb, Th, Ti, Tl, Tm, U, Y, Yb, Zn and Zr mass fraction in BPH and normal prostate glands of adult males is shown in Table 2. When obtained results were compared with data of literature a number of values for trace element mass fractions were not expressed on a dry mass basis by the authors of the cited references. However, these values were calculated using the medians of published data for water – 83% and ash – 1% (on wet mass basis) contents in nonhyperplastic prostate of adult men [36,37], and also for water – 80% in hyperplastic prostate [38].

To estimate the effect of age on the trace element mass fractions in BPH gland two age groups were examined: The first comprised persons with ages ranging from 56 to 65 years (mean age 62±3 years, n=18) and the second comprised those with ages ranging from 66 to 87 years (mean age 70±5 years, n=14). The means, the ratios of means and the reliability of difference between mean values of trace element mass fractions and ratios in two age groups are presented in Table 3.

Table 1. Comparison of mean values (M±SEM) of the trace element mass fraction (mg/kg, dry mass basis) in BPH and normal prostate

Element	Symbol	BPH 56-78 year n=32	Normal 44-87 year n=32	Student's t-test *p* =	Ratio BPH to normal
Silver	Ag	0.0415±0.0090	0.0371±0.0060	0.687 (NS)	1.12
Aluminum	Al	24.4±3.2	34.2±3.7	0.054 (NS)	0.71
Gold	Au	0.00257±0.00077	0.00412±0.00078	0.168 (NS)	0.63
Boron	B	1.51±0.26	1.04±0.18	0.160 (NS)	1.45
Berillium	Be	0.00092±0.00004	0.00094±0.00008	0.810 (NS)	0.98
Bismuth	Bi	0.140±0.042	0.027±0.011	0.024	5.19
Bromine	Br	30.6±3.4	28.5±2.9	0.629 (NS)	1.07
Cadmium	Cd	1.07±0.43	1.10±0.13	0.947 (NS)	0.97
Cerium	Ce	0.0128±0.0019	0.0281±0.0043	0.0028	0.46
Cobalt	Co	0.0617±0.0084	0.0459±0.0066	0.148 (NS)	1.34
Cromium	Cr	1.00±0.10	0.53±0.07	0.00054	1.89
Cesium	Cs	0.0235±0.0025	0.0339±0.0035	0.0198	0.69
Dysprosium	Dy	0.00156±0.00024	0.00287±0.00051	0.0272	0.54
Erbium	Er	0.00072±0.00013	0.00145±0.00024	0.0115	0.50
Iron	Fe	133±11	109±9	0.098 (NS)	1.22
Gadolinium	Gd	0.00153±0.00027	0.00281±0.00041	0.0140	0.54
Hg	Hg	0.259±0.029	0.052±0.008	0.0000004	4.98
Holmium	Ho	0.00032±0.00005	0.00054±0.00008	0.0217	0.59
Lanthanum	La	0.0385±0.0073	0.0713±0.0183	0.00894	0.54
Lithium	Li	0.0385±0.0073	0.0425±0.0057	0.667 (NS)	0.91
Manganese	Mn	1.19±0.09	1.32±0.08	0.314 (NS)	0.90
Molybdenum	Mo	0.167±0.009	0.285±0.040	0.00763	0.59
Niobium	Nb	0.0102±0.0079	0.0055±0.0012	0.572 (NS)	1.85
Neodymium	Nd	0.0062±0.0009	0.0129±0.0020	0.00539	0.48
Nickel	Ni	3.22±1.06	3.12±0.53	0.933 (NS)	1.03
Pb	Pb	0.69±0.16	2.46±0.58	0.00612	0.28
Praseodymium	Pr	0.00149±0.00027	0.00331±0.00050	0.00314	0.45
Rubidium	Rb	14.3±0.8	13.0±0.9	0.265 (NS)	1.10
Antimony	Sb	0.163±0.036	0.039±0.006	0.00282	4.18
Scandium	Sc	0.0257±0.0040	0.0310±0.0057	0.460 (NS)	0.83
Selenium	Se	1.11±0.07	0.76±0.05	0.000278	1.46
Samarium	Sm	0.00143±0.00038	0.00262±0.00036	0.0308	0.55
Tin	Sn	0.108±0.029	0.322±0.066	0.00547	0.34
Terbium	Tb	0.00017±0.00003	0.00038±0.00006	0.00366	0.44
Thorium	Th	0.00180±0.00034	0.00327±0.00077	0.091 (NS)	0.55
Titanium*	Ti*	1.52±0.20	2.63±0.64	0.112 (NS)	0.58
Thallium	Tl	0.00202±0.00057	0.00136±0.00015	0.286 (NS)	1.49
Thulium	Tm	0.00015±0.00002	0.00024±0.00004	0.0400	0.63
Uranium	U	0.0021±0.0009	0.0070±0.0022	0.0489	0.30
Yttrium	Y	0.0071±0.0012	0.0187±0.0044	0.0174	0.38
Ytterbium	Yb	0.00083±0.00020	0.00137±0.00026	0.101 (NS)	0.61
Zinc	Zn	1271±102	1060±142	0.233 (NS)	1.20
Zirconium	Zr	0.091±0.036	0.037±0.006	0.172 (NS)	2.46

M – arithmetic mean, SEM – standard error of mean, NS – not significant difference
** Titanium tools were used for sampling and sample preparation*

Table 2. Median, minimum and maximum value of means of trace element mass fractions (mg/kg, on dry mass basis) in BPH gland according to data from the literature in comparison with this works' results

Element	Published data reference			This work
	Median of means, (n^a)	Minimum of means M or M±SD, (n^b)	Maximum of means M or M±SD, (n^b)	M±SD n=32
Ag	-	-	-	0.042±0.042
Al	-	-	-	24±10
Au	-	-	-	0.0026±0.0025
B	-	-	-	1.51±0.79
Be	-	-	-	0.00092±0.00014
Bi	-	-	-	0.140±0.139
Br	23.3 (2)	18±9 (27)[19]	21.5±13 (9)[20]	30.6±17.2
Cd	1.3 (12)	0.395±0.200 (7)[21]	1641 ±960 (60) [22]	1.07±1.42
Ce	-	-	-	0.0128±0.0063
Co	19 (1)	19.0±1.5 (1)[23]	19.0±1.5 (1)[23]	0.062±0.038
Cr	99 (2)	6.5±0.5 (2)[23]	191±17 (27)[19]	1.00±0.44
Cs	-	-	-	0.0235±0.0081
Dy	-	-	-	0.00156±0.00080
Er	-	-	-	0.00072±0.00042
Fe	197 (10)	5.9±0.4 (8)[24]	1345±95 (27)[19]	133±63
Gd	-	-	-	0.00153±0.00088
Hg	-	-	-	0.259±0.136
Ho	-	-	-	0.00032±0.00016
La	-	-	-	0.0187±0.0096
Li	-	-	-	0.039±0.024
Mn	9 (7)	6.5 (-)[25]	23±13 (27)[19]	1.19±0.31
Mo	-	-	-	0.167±0.029
Nb	-	-	-	0.010±0.026
Nd	-	-	-	0.0062±0.0029
Ni	22.5 (3)	1.35±1.00 (27)[21]	48.5±9.0 (27)[19]	3.22±3.51
Pb	125 (1)	125±35 (25)[26]	125±35 (25)[26]	0.69±0.53
Pr	-	-	-	0.00149±0.00090
Rb	15.0 (2)	14.9±1.0 (43)[27]	15±5 (10)[28]	14.3±4.3
Sb	-	-	-	0.163±0.167
Sc	-	-	-	0.026±0.016
Se	0.98 (10)	0.76±0.37 (10)[29]	11.5±6.0 (27)[19]	1.11±0.33
Sm	-	-	-	0.0014±0.0013
Sn	-	-	-	0.108±0.097
Tb	-	-	-	0.00017±0.00008
Th	-	-	-	0.0018±0.0011
Ti	141 (1)	141±16 (27)[19]	141±16 (27)[19]	1.52±0.66*
Tl	-	-	-	0.0020±0.0018
Tm	-	-	-	0.00015±0.00007
U	-	-	-	0.0021±0.0031
Y	-	-	-	0.0071±0.0038
Yb	-	-	-	0.00083±0.00066
Zn	725 (39)	55±25 (23)[30]	3800±65 (10)[31]	1271±623
Zr	-	-	-	0.091±0.115

M – arithmetic mean, SD – standard deviation, n^a – No. of references contribution to this value, n^b – No. of samples, "–" no data available,
** Titanium tools were used for sampling and sample preparation*

Table 3. Differences between mean values (M±SEM) of the trace element mass fraction (mg/kg, dry mass basis) in hyperplastic prostate glands of two age groups

Element	BPH			Ratio group 2/ Group 1
	Age group 1 56-65 year (n=18)	Age group 2 66-78 year (n=14)	Student's t-test *p* =	
Ag	0.0309±0.0061	0.0502±0.0156	0.267 (NS)	1.62
Al	24.8±5.4	24.1±4.1	0.921 (NS)	0.97
Au	0.0037±0.0016	0.0018±0.0.0002	0.289 (NS)	0.49
B	1.60±0.47	1.47±0.35	0.831 (NS)	0.92
Be	0.000940±0.000060	0.000900±0.000063	0.657 (NS)	0.96
Bi	0.123±0.050	0.154±0.068	0.723 (NS)	1.25
Br	33.8±5.8	28.3±4.1	0.446 (NS)	0.84
Cd	0.50±0.13	1.56±0.75	0.218 (NS)	3.12
Ce	0.0144±0.0035	0.0115±0.0020	0.498 (NS)	0.80
Co	0.0456±0.0035	0.0748±0.0102	0.068 (NS)	1.64
Cr	0.82±0.08	1.17±0.11	0.087 (NS)	1.43
Cs	0.0280±0.0046	0.0198±0.0015	0.150 (NS)	0.71
Dy	0.00140±0.00039	0.00169±0.00042	0.584 (NS)	1.21
Er	0.00075±0.00025	0.00069±0.00013	0.837 (NS)	0.92
Fe	138±20	129±11	0.651 (NS)	0.93
Gd	0.00140±0.00027	0.00163±0.00046	0.671 (NS)	1.16
Hg	0.228±0.038	0.285±0.042	0.328 (NS)	1.25
Ho	0.000258±0.000075	0.000373±0.000058	0.260 (NS)	1.45
La	0.0190±0.0028	0.0184±0.0058	0.929 (NS)	0.97
Li	0.041±0.013	0.036±0.009	0.776 (NS)	0.88
Mn	1.16±0.15	1.22±0.13	0.795 (NS)	1.05
Mo	0.166±0.012	0.168±0.014	0.901 (NS)	1.01
Nb	0.0195±0.0174	0.0024±0.0006	0.380 (NS)	0.12
Nd	0.0066±0.0017	0.0058±0.0009	0.709 (NS)	0.88
Ni	5.06±2.1	1.68±0.20	0.188 (NS)	0.33
Pb	0.65±0.24	0.72±0.23	0.837 (NS)	1.11
Pr	0.00166±0.00053	0.00135±0.00027	0.621 (NS)	0.81
Rb	13.4±1.2	15.0±1.0	0.305 (NS)	1.12
Sb	0.183±0.073	0.146±0.024	0.642 (NS)	0.80
Sc	0.0171±0.0036	0.0333±0.0058	0.036	1.95
Se	1.11±0.07	1.10±0.12	0.917 (NS)	0.99
Sm	0.00130±0.00048	0.00153±0.00060	0.769 (NS)	1.18
Sn	0.054±0.006	0.153±0.047	0.089 (NS)	2.83
Tb	0.000154±0.000043	0.000177±0.000031	0.678 (NS)	1.15
Th	0.00178±0.00045	0.00182±0.00053	0.959 (NS)	1.02
Ti*	1.48±0.32	1.57±0.27	0.841 (NS)	1.06
Tl	0.0016±0.0003	0.0025±0.0011	0.471 (NS)	1.56
Tm	0.000136±0.000036	0.000163±0.000027	0.560 (NS)	1.20
U	0.0031±0.0020	0.0012±0.0004	0.414 (NS)	0.39
Y	0.0068±0.0023	0.0074±0.0012	0.821 (NS)	1.09
Yb	0.00076±0.00040	0.00088±0.00019	0.790 (NS)	1.16
Zn	1125±106	1443±180	0.139 (NS)	1.28
Zr	0.135±0.089	0.062±0.019	0.476 (NS)	0.46

M – arithmetic mean, SEM – standard error of mean, NS - not significant difference

Table 4 depicts the data of inter-correlation calculations (values of *r* – coefficient of correlation) including pairs of selected Bi, Cr, Hg, Se, and Zn with all other trace elements identified in BPH and normal prostate glands.

4. DISCUSSION

The INAA-LLR and ICP-MS allowed determine the mean mass fractions of 10 (Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn) and 41 (Ag, Al, Au, B, Be, Bi, Br, Cd, Ce, Co, Cr, Cs, Dy, Er, Gd, Hg, Ho, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Se, Sm, Sn, Tb, Th, Ti, Tl, Tm, U, Y, Yb, Zn and Zr) trace elements, respectively, in the samples of BPH and normal prostate glands. Thus, the use two analytical methods allowed estimate the mass fractions of 43 trace elements. Moreover, good agreement was found between the mean values of the Ag, Co, Cr, Hg, Rb, Sb, Se, and Zn mass fractions determined by both INAA-LLR and ICP-MS indicating complete digestion of the

Table 4. Intercorrelations of selected pairs of the trace element mass fractions in BPH and normal prostate glands of adults (*r* – coefficient of correlation)

El	BPH					Normal prostate				
	Bi	**Cr**	**Hg**	**Se**	**Zn**	**Bi**	**Cr**	**Hg**	**Se**	**Zn**
Ag	-0.37	0.08	0.48	-0.45	0.75[a]	-0.23	-0.36	0.32	-0.18	0.15
Al	0.23	0.51	0.62	0.70	0.27	-0.08	-0.04	-0.09	-0.03	-0.14
Au	-0.10	0.07	0.31	0.12	0.07	-0.18	0.26	0.15	0.34	-0.18
B	0.40	0.09	-0.16	-0.10	-0.40	0.10	0.02	0.09	-0.12	-0.15
Be	-0.05	0.37	0.53	0.05	0.34	0.14	-0.24	0.01	-0.27	0.20
Bi	**1.00**	0.13	0.02	0.34	-0.43	**1.00**	-0.26	-0.14	0.01	-0.04
Br	-0.34	-0.15	-0.39	-0.23	-0.03	-0.38	0.10	-0.27	-0.25	-0.33
Cd	0.36	0.59	0.42	0.26	0.36	0.07	0.29	0.04	-0.11	-0.27
Ce	0.04	0.38	0.81[a]	0.41	0.31	0.65[b]	-0.10	-0.03	-0.03	-0.13
Co	0.34	0.36	0.47	0.38	0.31	0.17	-0.11	-0.07	-0.12	-0.06
Cr	0.13	**1.00**	0.39	0.51	0.24	-0.26	**1.00**	-0.06	0.48	0.15
Cs	0.09	-0.31	0.47	0.36	-0.07	0.17	0.34	0.27	0.32	0.14
Dy	-0.02	0.66	0.35	0.53	0.27	-0.06	-0.15	-0.19	-0.13	-0.16
Er	0.04	0.58	0.44	0.47	0.08	-0.09	-0.09	-0.25	-0.08	-0.16
Fe	0.13	0.13	0.27	-0.30	-0.15	0.12	0.34	0.36	0.44	0.27
Gd	-0.22	0.26	0.35	0.41	0.33	0.20	-0.15	-0.21	-0.10	-0.20
Hg	0.02	0.39	**1.00**	-0.11	0.54	-0.14	-0.06	**1.00**	0.41	0.41
Ho	0.04	0.75[a]	0.35	0.27	0.43	-0.13	-0.08	-0.19	-0.05	-0.21
La	0.49	0.06	0.02	-0.01	-0.29	-0.08	-0.22	-0.22	-0.17	-0.01
Li	0.28	-0.08	0.32	0.24	-0.13	0.01	0.31	-0.01	0.18	-0.16
Mn	-0.19	-0.10	0.48	-0.56	0.50	-0.08	-0.01	0.01	0.11	-0.02
Mo	0.15	0.74[a]	0.18	-0.16	0.14	-0.23	0.16	0.28	-0.14	-0.05
Nb	-0.30	0.40	0.11	0.25	-0.01	-0.17	-0.02	-0.34	-0.22	-0.32
Nd	0.07	0.42	0.82[a]	0.29	0.32	0.56[a]	-0.13	-0.15	-0.05	-0.18
Ni	-0.38	0.46	0.03	0.05	-0.05	-0.21	-0.15	0.45	-0.16	0.06
Pb	-0.15	-0.15	0.43	0.12	0.33	0.27	-0.07	0.35	-0.05	-0.03
Pr	0.07	0.27	0.67	0.33	0.20	0.63[a]	-0.12	-0.06	-0.04	-0.15
Rb	-0.13	0.09	0.24	0.09	0.19	0.12	0.16	0.27	0.27	0.36
Sb	0.42	-0.24	0.25	0.16	-0.12	-0.27	-0.05	0.01	-0.04	-0.03
Sc	-0.82[a]	0.45	0.62	-0.30	0.72	0.59[a]	0.08	0.53[a]	0.62[a]	0.62[a]
Se	0.34	0.51	-0.11	**1.00**	-0.29	0.01	0.48	0.41	**1.00**	0.28
Sm	0.06	0.70	0.65	0.61	0.42	0.41	-0.14	-0.12	-0.04	-0.19
Sn	-0.56	-0.44	-0.23	-0.31	0.26	0.06	-0.21	0.19	-0.13	-0.10
Tb	0.09	0.25	0.53	0.05	0.10	0.11	-0.19	-0.22	-0.05	-0.20
Th	-0.17	0.26	0.44	0.52	0.31	0.52[a]	0.01	-0.20	0.04	-0.15
Ti*	-0.23	0.49	0.21	-0.08	0.45	-0.09	0.06	0.05	-0.11	0.25
Tl	0.66	0.03	-0.17	-0.13	-0.48	-0.25	0.34	0.36	0.65[b]	0.54[a]
Tm	-0.08	0.71	0.44	0.35	0.40	-0.15	-0.11	-0.11	-0.10	-0.20
U	0.37	-0.08	0.58	0.32	-0.15	-0.10	0.07	-0.01	-0.29	0.01
Y	0.05	0.74[a]	0.42	0.46	0.19	-0.03	-0.29	0.01	-0.21	-0.03
Yb	-0.11	0.62	0.25	0.50	0.17	-0.12	-0.11	-0.24	-0.09	-0.17
Zn	-0.43	0.24	0.54	-0.29	**1.00**	-0.04	0.15	0.41	0.28	**1.00**
Zr	-0.20	0.08	0.17	0.02	0.11	-0.16	0.10	-0.17	0.09	-0.08

El - elements, Statistically significant difference: [a] - p≤0.01, [b] - p≤0.001

prostate samples (for ICP-MS techniques) and correctness of all results obtained by the two methods. The fact that the results for the CRM obtained in the present work were in good agreement with the certified values and within the corresponding 95% confidence intervals [15,17] suggests an acceptable accuracy of the measurements performed on the prostate samples.

In the hyperplastic prostates an increase in mass fraction of Ag, B, Bi, Co, Cr, Fe, Hg, Nb, Rb, Sb, Se, Tl, Zn, and Zr in comparison with the normal prostates was observed (Table 1). In particular, a significant higher level of Bi, Cr, Hg, Sb, and Se was found in BPH gland (Table 1). For example, in prostate glands of patients with BPH the means of Bi, Hg, and Sb mass fraction was 4-5 times greater than in controls. Such metal as Bi, Co, Cr, Fe, Nb, Sb, and Tl binds more tightly within the prostatic cells than within prostatic fluid [39-42]. Thus, because the major characteristic of BPH is an overgrowth of the prostatic cells, becomes clear why an increase in the prostatic

Bi, Co, Cr, Fe, Nb, Sb, and Tl mass fractions has respect to a hyperplastic transformation. Trace element Se is a well known and important non-enzymatic antioxidant that reduces the activity of number of physiologically generated oxygen radicals. High levels of such trace elements as Co, Cr, Hg, Fe and Zn and an imbalance with other transition metals (for example, low level of Mn) indicate indirectly an increased oxidative stress in BPH tissue. Thus, it might be supposed that the accession of oxidative stress in BPH gland was accompanied by the elevated level of Se.

In the hyperplastic prostates a significant decrease in mass fraction of Ce, Cs, Dy, Er, Gd, Ho, La, Mo, Nd, Pb, Pr, Sm, Sn, Tb, Tm, U, and Y in comparison with the normal prostates was also found (Table 1). The biochemical reason behind the low levels of these element mass fractions in BPH gland requires further study for a more complete understanding. No statistically significant differences between the mean values of all other trace element mass fractions determined in this study (Ag, Al, Au, B, Be, Br, Cd, Co, Fe, Li, Mn, Nb, Ni, Rb, Sc, Th, Ti, Tl, Yb, Zn, and Zr) for BPH and normal prostates were shown (Table 1).

The obtained mean values for Cd, Fe, Ni, Rb, Se, and Zn mass fractions in BPH gland, as shown in Table 2, agree well with median of means cited by other researches. Mean value for Br mass fraction is somewhat higher than the maximum mean value of previously reported data. The means of this work for Co, Cr, Mn, Pb, and Ti mass fractions are from one to two orders of magnitude lower, than previously reported minimal results. No published data referring to Ag, Al, Au, B, Be, Bi, Ce, Cs, Dy, Er, Gd, Hg, Ho, La, Li, Mo, Nb, Nd, Pr, Sb, Sc, Sm, Sn, Tb, Th, Tl, Tm, U, Y, Yb, and Zr mass fractions in BPH gland were found.

In previous publications [15-17,43-47] it was shown that in the histologically normal prostates of males in the sixth to ninth decades, the magnitude of mass fractions of all trace elements were maintained at near constant levels. No age-related differences in mass fraction of trace elements in the hyperplastic prostate glands of men aged from 56 to 78 years were found in this study (Table 3). The only exclusion was the mass fraction of Sc. The mean mass fraction of Sc in the prostate glands of males aged 66-78 years was almost 2 times higher ($p \leq 0.036$) than in the prostate glands of males aged 56-65 years.

In control group of males a statistically significant ($p \leq 0.01$) direct correlation was found, for example, between the prostatic Zn and Sc (r = 0.62), and Zn and Tl (r = 0.54), between the prostatic Se and Sc (r = 0.62), and Se and Tl (r = 0.65), between the prostatic Bi and Ce (r = 0.65), Bi and Nd (r = 0.56), Bi and Pr (r = 0.63), Bi and Sc (r = 0.59), and Bi and Th (r = 0.52), and between the prostatic Hg and Sc (r = 0.53) (Table 3). In hyperplastic prostates some correlations between trace elements found in the control group are no longer evident, for example, correlations for some pairs with Se, but other correlations (direct Zn-Al, Hg-Ce, Hg-Nd, Cr-Ho, Cr-Mo, Cr-Y, and reverse Bi-Sc) are arisen (Table 3). Thus, accepting the levels and relationships of trace element mass fractions in prostate glands of males in the control group as a norm, it can be concluded that with a hyperplastic transformation the levels and relationships of chemical elements in prostate significantly changed. No published data referring to correlations between trace elements mass fractions in BPH gland were found.

Numerous *in vitro* and *in vivo* studies have evidenced that the disturbed homeostasis of Zn, Fe, and Se can play a very important role in the mechanism of uncontrolled cellular hyperplasia [13]. The high level of Zn, Fe, Se and some other trace element contents found just in the prostate gland [6-10] cannot be regarded as pure chance. It indicates that these elements must play here a very essential role for preserving the normal function of prostate cells and retaining the balance between their proliferation and physiological death (apoptosis). Exists an opinion that the elderly male population is predisposed to conditions of Zn, Fe, Se and some other trace elements deficiencies [12,48-51], which can increase this population's susceptibility to BPH. Since iodine deficiency can make the thyroid gland expand in size, it is thought that a Zn deficiency may also cause the prostate gland to increase in size. According to the proponents of dietary supplemental Zn usage, in the absence of Zn supplements, cellular Zn uptake will be depressed and Zn levels in normal prostate cells will be reduced [14,52]. This study data reveal that there are no any differences between Zn and Fe mass fraction in the prostate of healthy individuals and patients with BPH. Moreover, the mean level of Se content in hyperplastic prostates significantly higher then in

nonhyperplastic glands. Thus, “the potential role Zn, Fe, and Se deficiency” in the prostate [13] has not been confirmed as being involved in the etiology of BPH.

To clarify the role of chemical elements in prostate hyperplasia, the prostatic levels of 43 trace element mass fractions and the interrelationships of these trace element mass fractions were studied in the present work. However, there are many other chemical elements involved in normal metabolism and pathophysiology of the prostate gland. Thus, further studies are needed to extend the list of chemical elements measured using an up-to-date analytical technology. An estimation of the significance of prostatic chemical element levels as the BPH markers is also planed in the future investigations.

5. CONCLUSION

This work revealed that there is a significant tendency for an increase in Bi, Cr, Hg, Sb, and Se mass fraction in hyperplastic prostates. Present study finding of trace element contents and correlation between pairs of trace element mass fractions indicates that there is a great disturbance of prostatic chemical element relationships in BPH gland. Because the biochemical changes preceded the morphological transformations, it can be concluded that not only a high level of some trace elements but also a great disturbance in the relationships of trace elements in prostatic parenchyma is a pathogenetic factor of BPH.

Obtained data did not confirm a critical role of Cd and Pb accumulation in the pathogenesis of BPH. The potential age-related Zn, Fe, and Se deficiency in the prostate has not been found as being involved in the etiology of BPH. This work data cast doubts on a beneficial effect of the Zn, Fe, and Se supplementations on BPH prevention and treatment. Additional studies of other major, minor and trace elements in BPH gland are planned.

CONSENT

Both authors declare that written informed consent was obtained from the patient for publication of this paper.

ETHICAL APPROVAL

All studies were approved by the Ethical Committee of the Medical Radiological Research Center, Obninsk. Ethics clearance is in the journals number 12 (10.12.2010).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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