Asian Journal of Urology (2019) 6, 275–289

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Original Article

Comparison of 66 chemical element contents in normal and benign hyperplastic prostate

Vladimir Zaichick [a,*], **Sofia Zaichick** [b]

[a] *Radionuclide Diagnostics Department, Medical Radiological Research Centre, Kaluga Region, Russia*
[b] *Laboratory of Dr. Gabriela CaraveoPiso, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA*

Received 25 December 2016; received in revised form 28 April 2017; accepted 21 July 2017
Available online 6 December 2017

KEYWORDS
Benign prostate hyperplasia;
Prostatic chemical element contents;
Trace element supplementations;
Energy dispersive X-ray fluorescence analysis;
Neutron activation analysis;
Inductively coupled plasma atomic emission and mass spectrometry

Abstract *Objective:* The aim of this study was to clarify the differences between the prostatic levels of chemical elements in patients with benign prostatic hyperplasia (BPH) and healthy male.
Methods: We evaluated the prostatic level of 66 chemical elements in 43 patients with BPH and 37 healthy males. Measurements were performed using five instrumental analytical methods.
Results: In the hyperplastic prostates, we have observed a significant increase in the mean level of Bi, Cr, Hg, K, Sb, and Se accompanied a significant decrease in the mean level of Al, Ce, Cs, Dy, Er, Gd, Ho, La, Mo, Nd, Pb, Pr, Sm, Sn, Tb, Tm, U, and Y. No differences were found in the mean prostatic level of other chemical elements including Ag, Al, Au, B, Ba, Be, Br, Ca, Cd, Co, Cu, Fe, Li, Mg, Mn, Na, Nb, Ni, P, Rb, S, Sc, Si, Th, Ti, Tl, Yb, Zn, and Zr between BPH patients and healthy males.
Conclusions: The finding of chemical element contents and correlation between pairs of chemical element mass fractions indicates that there is a great disturbance of prostatic chemical element metabolism in BPH gland. Trace elements Bi, Cr, Hg, K, Sb, and Se may be regarded as the possible tissue biomarkers of hyperplastic transformation of prostate 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 tissue has not been found as being involved in the etiology of BPH.

* Corresponding author.
E-mail addresses: vezai@obninsk.com (V. Zaichick), szaitc1@uic.edu (S. Zaichick).
Peer review under responsibility of Second Military Medical University.

https://doi.org/10.1016/j.ajur.2017.11.009

1. Introduction

Benign prostatic hyperplasia (BPH) represents the most common age-related urologic disease. Prostatic tissue 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 aged 40—50 years, in over 70% at 60 years and in greater than 90% of men over 70 years [2]. To date, we still have 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 our previous studies it was shown that the levels of calcium (Ca), zinc (Zn), and some other chemical elements in prostate tissue are the androgen-dependent parameters and play an important role in prostate functions [5—10]. Moreover, it is well known that many other chemical elements besides Ca, Zn 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, 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 tissue will be reduced [13,14].

On the other hand, in our previous studies it was found a significant tendency for an increase in level of bismuth (Bi), cadmium (Cd), chromium (Cr), mercury (Hg), thorium (Th), uranium (U), 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 Ca, as well as Zn, Cd, Cr, lead (Pb), and some other trace metals to BPH development and progression [18—20].

The chemical element contents in tissue of the hyperplastic prostate have been studied, producing contradictory results [21—35]. The majority of these data are based on measurements of processed tissue and in many studies tissue 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 a few hours. There is evidence that certain quantities of chemical elements are lost as a result of such treatment [36—38]. Moreover, only a few of these studies employed quality control using certified reference materials for determination of the chemical element mass fractions. Thus, the questions about the differences between chemical element contents in intact and BPH tissue remained open.

This work had five aims. The first was to assess the 66 chemical element mass fractions: Silver (Ag), aluminum (Al), arsenic (As), gold (Au), boron (B), barium (Ba), beryllium (Be), Bi, bromine (Br), Ca, Cd, cerium (Ce), cobalt (Co), Cr, cesium (Ce), coper (Cu), dysprosium (Dy), erbium (Er), europium (Eu), iron (Fe), gallium (Ga), gadolinium (Gd), hafnium (Hf), Hg, holmium (Ho), iridium (Ir), potassium (K), lanthanum (La), lithium (Li), lutecium (Lu), magnesium (Mg), manganese (Mn), molybdenum (Mo), sodium (Na), niobium (Nb), neodymium (Nd), nickel (Ni), phosphorus (P), Pb, palladium (Pd), praseodymium (Pr), platinum (Pt), rubidium (Rb), rhenium (Re), rhodium (Rh), sulphur (S), antimony (Sb), scandium (Sc), selenium (Se), silicon (Si), samarium (Sm), tin (Sn), strontium (Sr), tantalum (Ta), terbium (Tb), tellurium (Te), Th, titanium (Ti), thallium (Tl), thulium (Tm), U, vanadium (V), yttrium (Y), ytterbium (Yb), zinc (Zn), and zirconium (Zr) in normal and BPH prostate using energy dispersive X-ray fluorescence (EDXRF), instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR), instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides (INAA-LLR), inductively coupled plasma atomic emission spectrometry (ICP-AES), and inductively coupled plasma mass spectrometry (ICP-MS). The second aim was to find differences between the results of BPH prostate and the levels of chemical 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 investigate the dependence of chemical element contents from the age of BPH patients and the stage of disease. The final aim was to estimate the inter-correlations between chemical element mass fractions in hyperplastic prostate and to compare these results with data for non hyperplastic gland.

2. Patients and methods

All patients studied ($n = 43$) were hospitalized in the Urological Department of the Medical Radiological Research Centre. All patients of Medical Radiological Research Centre have signed informed consent. In all cases the diagnosis of BPH ($n = 20$ in the 1st stage of disease, $n = 16$ in 2nd stage, and $n = 7$ in 3rd stage) has been confirmed by clinical and morphological results obtained during studies of biopsy and resected materials. 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 38 to 83 years, the mean being 66 ± 8 years (mean $\pm$ SD). Using a titanium scalpel resected materials were divided into two portions to permit morphological study of prostatic tissue and to estimate their chemical element contents.

Intact prostates were removed at necropsy from 37 men (mean age 55 ± 11 years, range 41—87 years) 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 chemical element 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 chemical element analysis were weighed, they were freeze-dried and homogenized. The pounded sample weighing about 8 mg was applied to a piece of adhesive tape, which served as a sample backing for EDXRF analysis. The sample weighing about 10—100 mg was used for chemical element measurement by INAA-SLR. The samples for INAA-SLR were sealed separately in thin polyethylene films washed with acetone and rectified alcohol beforehand. The sealed samples were placed in labeled polyethylene ampoules. A sample weighing about 10—50 mg was used for chemical element measurement by instrumental NAA-LLR. The samples for NAA-LLR were wrapped separately in a high-purity aluminum foil washed with rectified alcohol beforehand and placed in a nitric acid-washed quartz ampoule.

The samples weighing about 10—100 mg for ICP-AES and ICP-MS were decomposed in autoclaves; 1.5 mL of concentrated HNO_3 (nitric acid at 65%, maximum of 0.0000005% Hg; GR, ISO, Merck, Darmstadt, Germany) and 0.3 mL of H_2O_2 (pure for analysis) were added to the prostate tissue samples, placed in one-chamber autoclaves (Ancon-AT2, Ltd., Moscow, Russia) and then heated for 3 h at 160—200°C. After autoclaving, they were cooled to room temperature and solutions from the decomposed samples were diluted with deionized water (up to 20 mL) and transferred to plastic measuring bottles. Simultaneously, the same procedure was performed in autoclaves without tissue samples (only $HNO_3+H_2O_2+$deionized water), and the resultant solutions were used as control samples.

For quality control, samples of the certified reference materials IAEA H-4 Animal Muscle from the International Atomic Energy Agency (IAEA), and also samples INCT-SBF-4 Soya Bean Flour, INCT-TL-1 Tea Leaves and INCT-MPH-2Mixed Polish Herbs from the Institute of Nuclear Chemistry and Technology (INCT, Warsaw, Poland) were analyzed simultaneously with the prostate tissue samples being investigated. All samples of CRM were treated in the same way as the prostate tissue samples. Detailed results of this quality assurance program were presented in earlier publications [32,33,39—43].

The mass fractions of Br, Fe, Rb, Sr, and Zn were measured by EDXRF, the mass fractions of Br, Ca, K, Mg, Mn, and Na—by NAA-SLR, the mass fractions of Ag, As, Au, Ba, Br, Cd, Ce, Co, Cr, Cs, Eu, Fe, Gd, Hf, Hg, La, Lu, Nd, Rb, Sb, Sc, Se, Sm, Sr, Ta, Tb, Th, U, Yb, Zn, and Zr—by NAA-LLR, the mass fractions of Al, B, Ba, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn—by ICP-AES, and the mass fractions of Ag, Al, As, Au, B, Be, Bi, Br, Cd, Ce, Co, Cr, Cs, Dy, Er, Eu, Ga, Gd, Hf, Hg, Ho, Ir, La, Li, Lu, Mn, Mo, Nb, Nd, Ni, Pb, Pd, Pr, Pt, Rb, Re, Sb, Se, Sm, Sn, Ta, Tb, Te, Th, Ti, Tl, Tm, U, Y, Yb, Zn, and Zr—by ICP-MS. Details of the analytical methods and procedures used here such as nuclear reactions, radionuclides, γ-energies, wavelength, isotopes, spectrometers, spectrometer parameters and operating conditions were presented in our earlier publications concerning the chemical elements of human prostate gland [32,33,39—43].

A dedicated computer program of INAA mode optimization was used [44]. Using the Microsoft Office Excel software to provide a summary of statistical results, the arithmetic mean, SD, SEM, minimum and maximum values, median, percentiles with 0.025 and 0.975 levels were calculated for all the chemical element mass fractions obtained. For elements investigated by two or more methods the mean of all results was used. The difference in the results between BPH and normal prostates, as well as between two age (38—65 and 66—83 years) groups and stage of disease (stage1—2 and 3) groups was evaluated by both parametric Student's t-test and non-parametric Wilcoxon-Mann-Whitney U-test. 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 BPH prostate tissue the Microsoft Office Excel was also used.

3. Results

All studies were approved by the Ethical Committee of the Medical Radiological Research Center, Obninsk.

The results for 66 elemental mass fractions in non-hyperplastic and BPH prostate glands measured by means of the five analytical methods were obtained in the study. However, the mass fractions of As, Eu, Ga, Hf, Ir, Lu, Pd, Pt, Re, Ta, and V (11 trace elements) were determined only for the few samples measured. The possible upper limit of the mean (≤M) for these elements was calculated as the average mass fraction for each element, using the value of the detection limit (DL) instead of the individual value, when the latter was found to be below the DL:

$$\leq M = \left(\sum_{i}^{n_i} C_i + DL \cdot n_j \right) \Big/ n$$

where C_i is the individual value of chemical element mass fractions in the i_{th} sample, n_i is the number of samples with a measured mass fraction above DL, n_j is the number of samples with a measured mass fraction below DL, and $n = n_i + n_j$ is the total number of investigatedsamples. Thus, the possible upper limit of the mean for As, Eu, Ga, Hf, Ir, Lu, Pd, Pt, Re, Ta, and V (mg/kg, dry mass basis) were: As ≤0.018, Eu ≤0.00054, Ga ≤0.081, Hf ≤0.018, Ir ≤0.00042, Lu ≤0.00022, Pd ≤0.0074, Pt ≤0.00059, Re ≤0.00100, Ta ≤0.0053, and V ≤0.22. Generally, the mass fractions of Rh and Te were lower than the corresponding DL (in mg/kg on a dry mass basis) <0.01 and <0.003, respectively. Thus, the all basic statistical parameters of chemical element mass fraction (the arithmetic mean, standard deviation, standard error of mean, minimum and maximum values, median, percentiles with 0.025 and 0.975 levels) in BPH and normal prostate glands were calculated for 53 chemical elements (Tables 1 and 2, respectively).

Arithmetic mean and SEM for determined 53 chemical elements mass fractions in hyperplastic (group of patients

Table 1 Basic statistical parameters of chemical element mass fraction (mg/kg, dry mass basis) in the BPH prostate gland ($n = 43$).

Element	Symbol	M	SD	SEM	Min	Max	Median	P0.025	P0.975
Silver	Ag	0.0402	0.0416	0.0087	0.0040	0.1850	0.0289	0.0046	0.1560
Aluminum	Al	24.4	10.2	3.2	8.4	38.2	25.6	10.0	38.2
Gold	Au	0.00257	0.00255	0.00077	0.00100	0.0100	0.00200	0.00100	0.00833
Boron	B	1.51	0.79	0.26	0.70	3.20	1.20	0.760	3.02
Barium	Ba	1.22	0.68	0.20	0.42	2.32	0.97	0.468	2.24
Beryllium	Be	0.00092	0.00014	0.00004	0.00070	0.00100	0.00100	0.00070	0.00100
Bismuth	Bi	0.140	0.139	0.042	0.005	0.400	0.079	0.006	0.367
Bromine	Br	30.4	17.2	3.3	5.5	77.0	25.9	5.8	62.9
Calcium	Ca	2032	547	165	1168	2762	1898	1173	2757
Cadmium	Cd	1.07	1.42	0.43	0.21	5.20	0.50	0.23	4.20
Cerium	Ce	0.0128	0.0063	0.0019	0.0040	0.0250	0.0110	0.0045	0.0238
Cobalt	Co	0.0615	0.0366	0.0080	0.0246	0.1700	0.0500	0.0268	0.1520
Cromium	Cr	0.991	0.434	0.097	0.046	2.270	0.986	0.262	1.850
Cesium	Cs	0.0235	0.0081	0.0025	0.0150	0.0450	0.0220	0.0153	0.0408
Coper	Cu	9.86	3.96	1.25	6.00	18.90	8.30	6.25	17.90
Dysprosium	Dy	0.00156	0.00080	0.00024	0.00042	0.00285	0.00157	0.00047	0.00283
Erbium	Er	0.00072	0.00042	0.00013	0.00018	0.00156	0.00064	0.00019	0.00144
Iron	Fe	141	84	14	56	405	117	57	379
Gadolinium	Gd	0.00153	0.00088	0.00027	0.00040	0.00370	0.00150	0.00043	0.00330
Mercury	Hg	0.254	0.135	0.028	0.086	0.520	0.248	0.088	0.517
Holmium	Ho	0.00032	0.00016	0.00005	0.00009	0.00055	0.00039	0.00010	0.00053
Potassium	K	14 472	2454	740	11 683	20 519	13 552	12 025	19 744
Lanthanum	La	0.0187	0.0096	0.0030	0.0100	0.0410	0.0160	0.0100	0.0374
Lithium	Li	0.0385	0.0242	0.0073	0.0130	0.0880	0.0300	0.0138	0.0855
Magnesium	Mg	1201	276	83	687	1585	1263	749	1552
Manganese	Mn	1.19	0.31	0.09	0.80	1.80	1.20	0.80	1.73
Molybdenum	Mo	0.167	0.029	0.009	0.130	0.220	0.170	0.130	0.215
Sodium	Na	11 612	2882	869	7762	15 503	10 564	7893	15 400
Niobium	Nb	0.0102	0.0262	0.0079	0.0010	0.0890	0.0020	0.0010	0.0680
Neodymium	Nd	0.00618	0.00293	0.00088	0.00200	0.01200	0.00600	0.00200	0.01130
Nickel	Ni	3.22	3.51	1.06	1.00	12.20	1.90	1.03	11.10
Phosphorus	P	7907	1385	418	6279	11 780	7547	6512	10888
Lead	Pb	0.686	0.526	0.159	0.190	1.700	0.520	0.203	1.660
Praseodymium	Pr	0.00149	0.00090	0.00027	0.00020	0.00340	0.00130	0.00028	0.00313
Rubidium	Rb	14.8	4.6	0.8	6.6	24.0	15.0	7.3	22.9
Sulphur	S	8787	1616	487	7671	13 507	8289	7726	12 401
Antimony	Sb	0.162	0.163	0.035	0.0110	0.7330	0.1240	0.0121	0.5830
Scandium	Sc	0.0257	0.0156	0.0040	0.0039	0.0543	0.0213	0.0050	0.0536
Selenium	Se	1.11	0.32	0.07	0.43	1.60	1.15	0.53	1.60
Silicon	Si	141	79	24	72	333	102	73	307
Samarium	Sm	0.00143	0.00125	0.00038	0.00020	0.00420	0.00120	0.00020	0.00388
Tin	Sn	0.108	0.097	0.029	0.030	0.300	0.060	0.033	0.295
Strontium	Sr	3.87	2.58	0.59	0.20	10.9	3.40	0.83	9.73
Terbium	Tb	0.00017	0.00008	0.00002	0.00007	0.00030	0.00016	0.00008	0.00030
Thorium	Th	0.00180	0.00111	0.00034	0.00050	0.00410	0.00140	0.00060	0.00380
Titanium[a]	Ti[a]	1.53	0.66	0.20	0.70	2.00	2.00	0.70	2.00
Thallium	Tl	0.00202	0.00180	0.00057	0.00080	0.00700	0.00165	0.00082	0.00592
Thulium	Tm	0.00015	0.00007	0.00002	0.00004	0.00026	0.00017	0.00004	0.00026
Uranium	U	0.00210	0.00311	0.00094	0.00033	0.01120	0.00097	0.00042	0.00914
Yttrium	Y	0.00709	0.00383	0.00115	0.00200	0.01500	0.00790	0.00200	0.01370
Ytterbium	Yb	0.00083	0.00066	0.00020	0.00010	0.00230	0.00070	0.00013	0.00213
Zinc	Zn	1112	613	83	312	3142	1038	316	2492
Zirconium	Zr	0.091	0.115	0.036	0.010	0.400	0.065	0.010	0.335

BPH, benign prostatic hyperplasia; M, arithmetic mean; Max, maximum value; Min, minimum value; P0.025, percentile with 0.025 level; P0.975, percentile with 0.975 level; SD, standard deviation; SEM, standard error of mean.

[a] Titanium tools were used for sampling and sample preparation.

Table 2 Basic statistical parameters of chemical element mass fraction (mg/kg, dry mass basis) in the normal prostate gland of males of ages 41–87 years ($n = 37$).

Element	Symbol	M	SD	SEM	Min	Max	Median	P0.025	P0.975
Silver	Ag	0.0380	0.0296	0.0056	0.0050	0.1550	0.0300	0.0084	0.0976
Aluminum	Al	34.1	17.7	3.5	9.6	73.3	29.0	12.0	70.8
Gold	Au	0.00412	0.00346	0.00078	0.00100	0.01060	0.00230	0.00100	0.01030
Boron	B	1.04	0.85	0.18	0.30	3.00	0.70	0.30	2.89
Barium	Ba	1.48	1.01	0.21	0.20	4.33	1.17	0.30	3.73
Beryllium	Be	0.00094	0.00035	0.00007	0.00070	0.00210	0.00075	0.00070	0.00187
Bismuth	Bi	0.029	0.056	0.011	0.001	0.205	0.006	0.001	0.200
Bromine	Br	34.6	17.3	3.2	12.0	80.7	30.9	12.4	68.3
Calcium	Ca	2428	1232	233	1180	6893	2195	1197	5553
Cadmium	Cd	1.12	0.64	0.13	0.32	2.40	0.99	0.32	2.39
Cerium	Ce	0.0309	0.0244	0.0050	0.00600	0.0960	0.0220	0.0060	0.0937
Cobalt	Co	0.0467	0.0354	0.0064	0.0165	0.2000	0.0400	0.0169	0.1300
Cromium	Cr	0.562	0.433	0.082	0.030	1.810	0.456	0.030	1.670
Cesium	Cs	0.0339	0.0170	0.0033	0.0100	0.0870	0.0300	0.0131	0.0720
Coper	Cu	9.85	4.66	0.97	4.10	22.20	8.30	4.98	19.80
Dysprosium	Dy	0.00293	0.00242	0.00049	0.00069	0.01040	0.00224	0.000696	0.00934
Erbium	Er	0.00148	0.00114	0.00023	0.00040	0.00530	0.00116	0.00045	0.00421
Iron	Fe	121	34	6	62	210	114	68	192
Gadolinium	Gd	0.00290	0.00199	0.00041	0.000600	0.00850	0.00235	0.000715	0.00735
Mercury	Hg	0.0521	0.0426	0.0075	0.0077	0.1470	0.0335	0.0165	0.1410
Holmium	Ho	0.00057	0.00040	0.00008	0.00016	0.00179	0.00045	0.00017	0.00139
Potassium	K	11 650	2340	434	6325	18 198	11 403	7352	15 489
Lanthanum	La	0.080	0.100	0.020	0.009	0.324	0.034	0.010	0.309
Lithium	Li	0.0419	0.0264	0.0055	0.0150	0.1010	0.0300	0.0161	0.1000
Magnesium	Mg	1071	409	76	447	2060	1017	520	1955
Manganese	Mn	1.32	0.42	0.09	0.75	2.80	1.30	0.84	2.23
Molybdenum	Mo	0.282	0.190	0.038	0.100	0.850	0.230	0.100	0.754
Sodium	Na	10 987	2158	394	6415	15 300	10 911	6719	15 151
Niobium	Nb	0.0054	0.0058	0.0012	0.0010	0.0200	0.0031	0.0010	0.0194
Neodymium	Nd	0.0137	0.0100	0.0021	0.0030	0.0420	0.0100	0.0030	0.0354
Nickel	Ni	3.10	2.49	0.51	0.20	9.50	2.85	0.37	8.29
Phosphorus	P	7617	1839	368	5969	14 838	7225	6017	11 741
Lead	Pb	2.39	2.85	0.56	0.15	10.70	0.83	0.18	9.39
Praseodymium	Pr	0.00353	0.00258	0.00053	0.00060	0.01060	0.00285	0.00072	0.00939
Rubidium	Rb	14.5	5.1	0.9	5.9	26.5	14.2	6.2	25.5
Sulphur	S	8657	1271	254	5662	12 567	8569	6680	11 366
Antimony	Sb	0.0427	0.0364	0.0063	0.0080	0.1580	0.0375	0.0096	0.1540
Scandium	Sc	0.0294	0.0236	0.0053	0.0046	0.0771	0.0200	0.0066	0.0768
Selenium	Se	0.748	0.266	0.047	0.318	1.490	0.735	0.348	1.440
Silicon	Si	102	55	11	32	235	94	37	205
Samarium	Sm	0.00267	0.00176	0.00035	0.00060	0.00700	0.00260	0.00066	0.00652
Tin	Sn	0.320	0.322	0.063	0.050	1.110	0.140	0.056	1.040
Strontium	Sr	2.47	1.98	0.41	0.87	8.90	1.60	0.92	6.87
Terbium	Tb	0.00039	0.00030	0.00006	0.00007	0.00120	0.00035	0.00007	0.00109
Thorium	Th	0.00335	0.00363	0.00074	0.00050	0.01720	0.00180	0.00056	0.01250
Titanium[a]	Ti[a]	2.82	3.07	0.64	0.70	13.70	1.82	0.70	10.10
Thallium	Tl	0.00138	0.00072	0.00015	0.00030	0.00300	0.00130	0.00042	0.00289
Thulium	Tm	0.00024	0.00017	0.00004	0.00004	0.00083	0.00020	0.00006	0.00062
Uranium	U	0.0070	0.0105	0.0021	0.0008	0.0381	0.0026	0.0008	0.0341
Yttrium	Y	0.0187	0.0217	0.0043	0.0005	0.0840	0.0100	0.0021	0.0765
Ytterbium	Yb	0.00141	0.00121	0.00025	0.00020	0.00510	0.00110	0.00032	0.00412
Zinc	Zn	1072	749	123	229	4298	915	244	2249
Zirconium	Zr	0.0358	0.0272	0.0055	0.0100	0.0900	0.0250	0.0100	0.0900

M, arithmetic mean; Max, maximum value; Min, minimum value; P0.025, percentile with 0.025 level; P0.975, percentile with 0.975 level; SD, standard deviation; SEM, standard error of mean.
[a] Titanium tools were used for sampling and sample preparation.

with BPH) and nonhyperplastic (age-matched control group) prostate were presented in Table 3. Table 3 also depicts the ratios of means and the differences between mean values of chemical element mass fractions in BPH and normal prostate. For some trace elements (Ag, Au, B, Ba, Bi, Cd, Ce, Co, Hg, La, Li, Nb, Ni, Pb, Sb, Sc, Si, Sn, Sr, Th, Ti, U, Y, and Zr) the big difference between mean and median was found (Tables 1 and 2). It meant that for these trace elements the distribution of individual results were not normal. It was a reason why the differences in the results between BPH and normal prostate were evaluated by both parametric Student's *t*-test and non-parametric Wilcoxon-Mann-Whitney *U*-test (Table 3).

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 glands of adult males is shown in Table 4. When our results were compared with data of literature a number of values for chemical element mass fractions were not expressed on a dry mass basis by the authors of the cited references. However, we calculated these values using the medians of published data for water (83%) and ash (1%) (on wet mass basis) contents in nonhyperplastic prostate of adult men [45,46], and also for water (80%) in BPH tissue [47].

To estimate the effect of age on the chemical element mass fractions in BPH tissue, we examined two age groups: The first comprised persons with ages ranging from 38 to 65 years (mean age 60 $\pm$ 6 years, $n = 22$) and the second comprised those with ages ranging from 66 to 83 years (mean age 73 $\pm$ 4 years, $n = 21$). The means, the ratios of means and the differences between mean values of chemical element mass fractions in two age groups, evaluated by both parametric Student's *t*-test and non-parametric Wilcoxon-Mann-Whitney *U*-test, are presented in Table 5.

To estimate the effect of stage of disease on the chemical element mass fractions in BPH tissue, we examined two groups: The first comprised persons with stages 1 and 2 combined (mean age 66 $\pm$ 8 years, $n = 36$) and the second comprised those with stage 3 (mean age 69 $\pm$ 7 years, $n = 7$). The means, the ratios of means and the differences between mean values of chemical element mass fractions, evaluated by both parametric Student's *t*-test and non-parametric Wilcoxon-Mann-Whitney *U*-test, in two groups were presented in Table 6.

Tables 7 and 8 depict the data of inter-correlation calculations (values of *r*—coefficient of correlation) including pairs of selected Bi, Cr, Cs,Hg, K, Mo, Pb, Sb, Se, Sn, and Zn with all other chemical elements identified in normal and BPH prostate glands, respectively.

4. Discussion

The use of five analytical methods allowed us to estimate the mass fractions of 66 non hyperplastic chemical elements in non hyperplastic and BPH prostate glands of males in the age range 38—87 years. Good agreement was found between the results obtained with non-destructive (EDXRF, NAA-SLR, and NAA-LLR) and destructive methods (ICP-AES and ICP-MS) for Ag, Br, Ca, Co, Cr, Fe, K, Mg, Mn, Na, Rb, Sb, Se, Sr, and Zn indicating complete digestion of the prostate samples (for ICP techniques) and correctness of all results obtained by the various methods. The fact that the elemental mass fractions (mean $\pm$ SD) of the certified reference materials obtained in the present work were in good agreement with the certified values and within the corresponding 95% confidence intervals [32,33,39—43] non hyperplastic suggests an acceptable accuracy of the measurements performed on our prostate samples (Tables 1 and 2).

In the hyperplastic prostates an increase in mass fractions of B, Bi, Co, Cr, Fe, Hg, K, Nb, Sb, Se, Si, Sr, Tl, and Zr in comparison with the normal prostates was observed (Table 3). In particular, a significant higher level of Bi, Cr, Hg, K, Sb, and Se was found in BPH gland (Table 3). For example, in prostate glands of patients with BPH the means of Bi, Hg, and Sb mass fraction were almost 4—5 times greater than in controls. Such elements as B, Bi, Co, Cr, Fe, Nb, Sb, Si, Tl, and Zr bind more tightly within the prostatic cells than within prostatic fluid [48—55]. Thus, because the major characteristic of BPH is an overgrowth of the prostatic cells, it becomes clear why an increase in the prostatic B, Bi, Co, Cr, Fe, Nb, Sb, Si, Tl, and Zr mass fractions has respect to a hyperplastic transformation. Trace element Se is an 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, we have observed an increase in mass fraction of K in comparison with the histologically normal prostates (Table 3). It is well known that K is the major cation of the intracellular fluid and cells are the main pool of this electrolyte in human body [47]. Thus, because the major characteristic of BPH is an overgrowth of the prostatic cells [1], becomes clear why an increase in the prostatic K mass fractions has respect to a hyperplastic transformation.

In the hyperplastic prostates a significant decrease in mass fraction of Al, 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 3). 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 chemical element mass fractions determined in this study (Ag, Au, B, Ba, Be, Br, Ca, Cd, Co, Cu, Fe, Li, Mg, Mn, Na, Nb, Ni, P, Rb, S, Sc, Si, Sr, Th, Ti, Tl, Yb, Zn, and Zr) for BPH and normal prostates were shown (Table 3).

The obtained mean values for Ca, Cd, Cu, Fe, Mg, P, Rb, Se, Sr, and Zn mass fractions in BPH gland, as shown in Table 4, agree well with median of means cited by other researches. Mean values for Br, K, and Na mass fraction were somewhat higher than the maximum of previously reported mean values while mean value for S were somewhat lower than the minimum of reported means. The means of this work for Co, Cr, Mn, Ni, Pb, and Ti mass fractions were almost from one to two orders of magnitude lower than previously

Table 3 Comparison of mean values of the chemical element mass fraction (mg/kg, dry mass basis) in BPH and normal prostate tissue (M ± SEM).

Element	BPH 38–83 years, *n* = 43	Normal 41–87 years, *n* = 37	*t*-test *p* value	U-test *p*-Value	Ratio (BPH/normal)
Ag	0.0402 ± 0.0087	0.0380 ± 0.0056	0.833	>0.05	1.06
Al	24.4 ± 3.2	34.1 ± 3.5	0.052	<0.05	0.72
Au	0.00257 ± 0.00077	0.00412 ± 0.00078	0.168	>0.05	0.62
B	1.51 ± 0.26	1.04 ± 0.18	0.160	>0.05	1.45
Ba	1.22 ± 0.20	1.48 ± 0.21	0.392	>0.05	0.82
Be	0.000918 ± 0.000042	0.000942 ± 0.000072	0.781	>0.05	0.97
Bi	0.140 ± 0.042	0.029 ± 0.011	**0.026**	**<0.01**	4.83
Br	30.4 ± 3.3	34.6 ± 3.2	0.359	>0.05	0.88
Ca	2,032 ± 165	2,428 ± 233	0.174	>0.05	0.84
Cd	1.07 ± 0.43	1.12 ± 0.13	0.927	>0.05	0.96
Ce	0.0128 ± 0.0019	0.0309 ± 0.0050	**0.0028**	**<0.01**	0.41
Co	0.0615 ± 0.0080	0.0467 ± 0.0064	0.153	>0.05	1.32
Cr	0.991 ± 0.097	0.562 ± 0.082	**0.0016**	**<0.01**	1.76
Cs	0.0235 ± 0.0025	0.0339 ± 0.0033	**0.017**	**<0.01**	0.69
Cu	9.86 ± 1.25	9.85 ± 0.97	0.996	>0.05	1.00
Dy	0.00156 ± 0.00024	0.00293 ± 0.00049	**0.018**	**<0.01**	0.53
Er	0.00072 ± 0.00013	0.00148 ± 0.00023	**0.0071**	**<0.01**	0.49
Fe	141 ± 14	121 ± 6	0.193	>0.05	1.17
Gd	0.00153 ± 0.00027	0.00290 ± 0.00041	**0.0081**	**<0.01**	0.53
Hg	0.254 ± 0.028	0.052 ± 0.008	**0.00000031**	**<0.01**	4.88
Ho	0.000321 ± 0.000048	0.000567 ± 0.000079	**0.012**	**<0.01**	0.57
K	14 471 ± 740	11 650 ± 434	**0.0042**	**<0.01**	1.24
La	0.0187 ± 0.0030	0.0799 ± 0.0196	**0.0047**	**<0.01**	0.23
Li	0.0385 ± 0.0073	0.0419 ± 0.0055	0.713	>0.05	0.92
Mg	1,201 ± 83	1,071 ± 76	0.257	>0.05	1.12
Mn	1.19 ± 0.09	1.32 ± 0.09	0.320	>0.05	0.90
Mo	0.167 ± 0.009	0.282 ± 0.038	**0.0067**	**<0.01**	0.59
Na	11 612 ± 869	10 987 ± 394	0.522	>0.05	1.06
Nb	0.0102 ± 0.0079	0.0054 ± 0.0012	0.564	>0.05	1.89
Nd	0.0062 ± 0.0009	0.0137 ± 0.0021	**0.0027**	**<0.01**	0.45
Ni	3.22 ± 1.06	3.10 ± 0.51	0.924	>0.05	1.04
P	7,907 ± 418	7,617 ± 368	0.606	>0.05	1.04
Pb	0.69 ± 0.16	2.39 ± 0.56	**0.0066**	**<0.01**	0.29
Pr	0.00149 ± 0.00027	0.00353 ± 0.00053	**0.0016**	**<0.01**	0.42
Rb	14.8 ± 0.8	14.5 ± 0.9	0.798	>0.05	1.02
S	8,787 ± 487	8,657 ± 254	0.816	>0.05	1.02
Sb	0.162 ± 0.035	0.0427 ± 0.0063	**0.0027**	**<0.01**	3.79
Sc	0.0257 ± 0.0040	0.0294 ± 0.0053	0.583	>0.05	0.87
Se	1.11 ± 0.07	0.748 ± 0.047	**0.000069**	**<0.01**	1.48
Si	141 ± 24	102 ± 11	0.156	>0.05	1.38
Sm	0.00143 ± 0.00038	0.00267 ± 0.00035	**0.023**	**<0.01**	0.54
Sn	0.108 ± 0.029	0.320 ± 0.063	**0.0046**	**<0.01**	0.34
Sr	3.87 ± 0.59	2.47 ± 0.41	0.061	>0.05	1.57
Tb	0.000166 ± 0.000025	0.000393 ± 0.000062	**0.0018**	**<0.01**	0.42
Th	0.00180 ± 0.00034	0.00335 ± 0.00074	0.066	>0.05	0.54
Ti[a]	1.52 ± 0.20	2.82 ± 0.64	0.064	>0.05	0.54
Tl	0.00202 ± 0.00057	0.00138 ± 0.00015	0.305	>0.05	1.46
Tm	0.000151 ± 0.000021	0.000241 ± 0.000035	**0.033**	**<0.05**	0.63
U	0.0021 ± 0.0009	0.0070 ± 0.0021	**0.042**	**<0.05**	0.30
Y	0.0071 ± 0.0012	0.0187 ± 0.0043	0.082	**<0.05**	0.38
Yb	0.00083 ± 0.00020	0.00141 ± 0.00025	0.074	>0.05	0.59
Zn	1,112 ± 83	1,072 ± 123	0.787	>0.05	1.04
Zr	0.091 ± 0.036	0.0358 ± 0.0055	0.167	>0.05	2.54

BPH, benign prostatic hyperplasia; M, arithmetic mean; SEM, standard error of mean; *t*-test, Student's *t*-test; *U*-test, Wilcoxon-Mann-Whitney *U*-test. Bold represents significant differences.

[a] Titanium tools were used for sampling and sample preparation.

Table 4 Median, minimum and maximum value of means of chemical element mass fractions (mg/kg, on dry mass basis) in BPH tissue according to data from the literature in comparison with this work's 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	—	—	—	0.040 ± 0.042
Al	—	—	—	24.4 ± 103.2
Au	—	—	—	0.0026 ± 0.0026
B	—	—	—	1.51 ± 0.79
Ba	—	—	—	1.22 ± 0.68
Be	—	—	—	0.00092 ± 0.00014
Bi	—	—	—	0.140 ± 0.139
Br	23.3 (2)	18 ± 9 (27) [21]	21.5 ± 13.0 (9) [22]	30 ± 17
Ca	3100 (6)	1000 (34) [23]	5100 ± 3200 (9) [22]	2032 ± 547
Cd	1.3 (12)	0.395 ± 0.200(7) [24]	1641 ± 960 (60) [25]	1.07 ± 1.41
Ce	—	—	—	0.0128 ± 0.0063
Co	19 (1)	19.0 ± 1.5 (1) [26]	19.0 ± 1.5 (1) [26]	0.062 ± 0.037
Cr	99 (2)	6.5 ± 0.5 (2) [26]	191 ± 17 (27) [21]	0.99 ± 0.43
Cs	—	—	—	0.0235 ± 0.0081
Cu	15 (12)	3 ± 1 (7) [24]	885 ± 80 (10) [27]	9.9 ± 4.0
Dy	—	—	—	0.00156 ± 0.00080
Er	—	—	—	0.00072 ± 0.00042
Fe	197 (10)	5.9 ± 0.4 (8) [28]	1345 ± 95 (27) [21]	141 ± 84
Gd	—	—	—	0.00153 ± 0.00088
Hg	—	—	—	0.25 ± 0.14
Ho	—	—	—	0.00032 ± 0.00016
K	7400 (5)	1010 ± 100 (27) [21]	12 800 ± 1900 (43) [29]	14 471 ± 2454
La	—	—	—	0.0187 ± 0.0095
Li	—	—	—	0.039 ± 0.024
Mg	820 (7)	566 ± 130 (25) [30]	1560 ± 50 (10) [31]	1201 ± 276
Mn	9 (7)	6.5 (—) [31]	23 ± 13 (27) [21]	1.19 ± 0.31
Mo	—	—	—	0.167 ± 0.029
Na	7800 (1)	7800 (34) [23]	7800 (34) [23]	11 612 ± 2882
Nb	—	—	—	0.010 ± 0.026
Nd	—	—	—	0.0062 ± 0.0029
Ni	22.5 (3)	1.35 ± 1.00 (27) [24]	48.5 ± 9.0 (27) [21]	3.2 ± 3.5
P	7600 (3)	7590 ± 1120 (43) [29]	19 300 ± 14 300 (9) [22]	7907 ± 1385
Pb	125 (1)	125 ± 35 (25) [31]	125 ± 35 (25) [31]	0.69 ± 0.53
Pr	—	—	—	0.00149 ± 0.00090
Rb	15.0 (2)	14.9 ± 1.0 (43) [32]	15 ± 5 (10) [33]	14.8 ± 4.6
S	37 400 (1)	37 400 ± 2100 (9) [22]	37 400 ± 2100 (9) [22]	8787 ± 1616
Sb	—	—	—	0.162 ± 0.163
Sc	—	—	—	0.0257 ± 0.0157
Se	0.98 (10)	0.76 ± 0.37 (10) [34]	11.5 ± 6.0 (27) [21]	1.11 ± 0.32
Si	—	—	—	141 ± 79
Sm	—	—	—	0.0014 ± 0.0013
Sn	—	—	—	0.108 ± 0.097
Sr	4.4 (2)	3.8 ± 0.6 (43) [32]	5.0 ± 3.0 (10) [33]	3.9 ± 2.6
Tb	—	—	—	0.000166 ± 0.000081
Th	—	—	—	0.0018 ± 0.0011
Ti[a]	141 (1)	141 ± 16 (27) [21]	141 ± 16 (27) [21]	1.52 ± 0.66
Tl	—	—	—	0.0020 ± 0.0018
Tm	—	—	—	0.000151 ± 0.000071
U	—	—	—	0.0021 ± 0.0031
Y	—	—	—	0.0071 ± 0.0038
Yb	—	—	—	0.00083 ± 0.00066
Zn	725 (39	55 ± 25 (23) [35]	3800 ± 65 (10) [30]	1112 ± 613
Zr	—	—	—	0.091 ± 0.115

BPH, benign prostatic hyperplasia; M, arithmetic mean; n^a, number of references contribution to this value; n^b, number of samples; SD, standard deviation; —, no data available.

[a] Titanium tools were used.

Table 5 Differences between mean values (M ± SEM) of the chemical element mass fraction (mg/kg, dry mass basis) in BPH.

Element	Age Group 1, 38–65 year ($n = 22$)	Age Group 2, 66–83 year ($n = 21$)	*t*-test *p*-Value	*U*-test *p*-Value	Ratio (Group 2/1)
Ag	0.0293 ± 0.0058	0.0502 ± 0.0156	0.228	>0.05	1.71
Al	24.8 ± 5.4	24.1 ± 4.1	0.921	>0.05	0.97
Au	0.0037 ± 0.0016	0.0017 ± 0.0002	0.289	>0.05	0.45
B	1.60 ± 0.47	1.47 ± 0.35	0.831	>0.05	0.92
Ba	1.24 ± 0.32	1.21 ± 0.29	0.950	>0.05	0.98
Be	0.00094 ± 0.00006	0.00090 ± 0.00006	0.657	>0.05	0.96
Bi	0.122 ± 0.050	0.154 ± 0.068	0.723	>0.05	1.26
Br	32.7 ± 5.1	28.4 ± 4.2	0.530	>0.05	0.87
Ca	2,104 ± 277	1972 ± 217	0.717	>0.05	0.94
Cd	0.49 ± 0.13	1.56 ± 0.75	0.218	>0.05	3.18
Ce	0.0144 ± 0.0035	0.0115 ± 0.0020	0.498	>0.05	0.80
Co	0.0469 ± 0.0048	0.0748 ± 0.0137	0.078	>0.05	1.59
Cr	0.815 ± 0.108	1.170 ± 0.150	0.070	<0.05	1.44
Cs	0.0280 ± 0.0046	0.0198 ± 0.0015	0.150	>0.05	0.71
Cu	7.88 ± 0.54	11.8 ± 2.2	0.146	>0.05	1.50
Dy	0.00140 ± 0.00039	0.00169 ± 0.00032	0.584	>0.05	1.21
Er	0.00075 ± 0.00025	0.00069 ± 0.00013	0.837	>0.05	0.92
Fe	145 ± 20	136 ± 20	0.749	>0.05	0.94
Gd	0.00140 ± 0.00027	0.00163 ± 0.00046	0.671	>0.05	1.16
Hg	0.219 ± 0.036	0.285 ± 0.042	0.250	>0.05	1.30
Ho	0.000258 ± 0.000072	0.000373 ± 0.000058	0.260	>0.05	1.45
K	15 438 ± 1584	13 666 ± 221	0.328	>0.05	0.89
La	0.0190 ± 0.0028	0.0184 ± 0.0058	0.929	>0.05	0.97
Li	0.041 ± 0.013	0.036 ± 0.009	0.776	>0.05	0.89
Mg	1255 ± 112	1156 ± 127	0.574	>0.05	0.92
Mn	1.16 ± 0.14	1.22 ± 0.13	0.795	>0.05	1.05
Mo	0.166 ± 0.012	0.168 ± 0.014	0.901	>0.05	1.01
Na	11 494 ± 1620	11 712 ± 1008	0.912	>0.05	1.02
Nb	0.0200 ± 0.0170	0.0024 ± 0.0006	0.380	>0.05	0.12
Nd	0.0066 ± 0.0017	0.0058 ± 0.0009	0.709	>0.05	0.88
Ni	5.06 ± 2.13	1.68 ± 0.20	0.188	>0.05	0.33
P	8445 ± 840	7458 ± 283	0.317	>0.05	0.88
Pb	0.65 ± 0.24	0.72 ± 0.23	0.837	>0.05	1.11
Pr	0.00166 ± 0.00053	0.00135 ± 0.00027	0.621	>0.05	0.81
Rb	14.4 ± 1.2	15.2 ± 1.1	0.630	>0.05	1.06
S	9504 ± 1 016	8189 ± 156	0.267	>0.05	0.86
Sb	0.178 ± 0.067	0.146 ± 0.024	0.651	>0.05	0.82
Sc	0.0171 ± 0.0036	0.0333 ± 0.0058	**0.036**	**<0.05**	1.95
Se	1.13 ± 0.07	1.10 ± 0.12	0.833	>0.05	0.97
Si	183 ± 45	105 ± 13	0.157	>0.05	0.57
Sm	0.00130 ± 0.00048	0.00153 ± 0.00060	0.769	>0.05	1.18
Sn	0.054 ± 0.006	0.153 ± 0.047	0.089	**<0.05**	2.83
Sr	3.89 ± 1.29	3.86 ± 0.62	0.983	>0.05	0.99
Tb	0.000154 ± 0.000043	0.000177 ± 0.000031	0.678	>0.05	1.15
Th	0.00178 ± 0.00045	0.00182 ± 0.00053	0.959	>0.05	1.02
Ti[a]	1.48 ± 0.32	1.57 ± 0.27	0.841	>0.05	1.06
Tl	0.00156 ± 0.00025	0.00248 ± 0.00114	0.471	>0.05	1.59
Tm	0.000136 ± 0.000036	0.000163 ± 0.000027	0.560	>0.05	1.20
U	0.0031 ± 0.0020	0.00125 ± 0.00036	0.414	>0.05	0.40
Y	0.0068 ± 0.0023	0.0074 ± 0.0012	0.821	>0.05	1.09
Yb	0.00076 ± 0.00040	0.00088 ± 0.00019	0.790	>0.05	1.16
Zn	1113 ± 88	1212 ± 141	0.239	>0.05	1.09
Zr	0.135 ± 0.089	0.062 ± 0.019	0.476	>0.05	0.46

BPH, benign prostatic hyperplasia; M, arithmetic mean; SEM, standard error of mean; *t*-test, Student's *t*-test; *U*-test, Wilcoxon-Mann-Whitney *U*-test; Bold represents significant differences.

[a] Titanium tools were used.

Table 6 Differences between mean values (M ± SEM) of the chemical element mass fraction (mg/kg, dry mass basis) in BPH of stage 1–2 and stage 3.

Element	Stage 1–2 (n = 36)	Stage 3 (n = 7)	t-test p-Value	U-test p-Value	Ratio (Stages 3/(1–2))
Ag	0.046 ± 0.012	0.027 ± 0.008	0.205	>0.05	0.59
Al	27.0 ± 4.1	20.5 ± 5.3	0.362	>0.05	0.76
Au	0.0032 ± 0.0012	0.0015 ± 0.0003	0.204	>0.05	0.47
B	1.68 ± 0.47	1.30 ± 0.18	0.480	>0.05	0.77
Ba	1.42 ± 0.30	0.88 ± 0.11	0.123	>0.05	0.62
Be	0.000957 ± 0.000043	0.000850 ± 0.000087	0.323	>0.05	0.89
Bi	0.181 ± 0.055	0.068 ± 0.053	0.175	>0.05	0.38
Br	28.0 ± 3.7	39.1 ± 6.2	0.159	>0.05	1.40
Ca	1967 ± 248	2147 ± 162	0.560	>0.05	1.09
Cd	1.27 ± 0.67	0.73 ± 0.22	0.470	>0.05	0.57
Ce	0.0147 ± 0.0025	0.0095 ± 0.0023	0.157	>0.05	0.65
Co	0.0667 ± 0.0106	0.0485 ± 0.0078	0.184	>0.05	0.73
Cr	0.990 ± 0.061	0.993 ± 0.310	0.992	>0.05	1.00
Cs	0.0259 ± 0.0035	0.0195 ± 0.0017	0.142	>0.05	0.75
Cu	9.63 ± 1.91	10.2 ± 1.6	0.826	>0.05	1.06
Dy	0.00157 ± 0.00027	0.00153 ± 0.00051	0.946	>0.05	0.97
Er	0.00077 ± 0.00016	0.00064 ± 0.00022	0.646	>0.05	0.83
Fe	146 ± 17	118 ± 10	0.161	>0.05	0.81
Gd	0.00137 ± 0.00020	0.00180 ± 0.00069	0.586	>0.05	1.31
Hg	0.287 ± 0.035	0.176 ± 0.033	**0.034**	>0.05	0.61
Ho	0.000333 ± 0.000057	0.000300 ± 0.000097	0.782	>0.05	0.90
K	15 356 ± 1012	12 924 ± 426	0.058	=0.05	0.84
La	0.0216 ± 0.0038	0.0120 ± 0.0020	0.056	=0.05	0.56
Li	0.0371 ± 0.0096	0.0408 ± 0.0127	0.828	>0.05	1.10
Mg	1188 ± 121	1223 ± 111	0.836	>0.05	1.03
Mn	1.22 ± 0.13	1.15 ± 0.14	0.738	>0.05	0.94
Mo	0.166 ± 0.007	0.170 ± 0.023	0.870	>0.05	1.02
Na	11 400 ± 1039	11 984 ± 1753	0.786	>0.05	1.05
Nb	0.0145 ± 0.0124	0.0026 ± 0.0010	0.377	>0.05	0.18
Nd	0.0069 ± 0.0012	0.0050 ± 0.0011	0.286	>0.05	0.72
Ni	3.27 ± 1.50	3.13 ± 1.55	0.948	>0.05	0.96
P	8305 ± 590	7211 ± 356	0.147	>0.05	0.87
Pb	0.71 ± 0.17	0.65 ± 0.35	0.890	>0.05	0.92
Pr	0.00164 ± 0.00037	0.00123 ± 0.00039	0.461	>0.05	0.75
Rb	14.8 ± 0.9	14.9 ± 1.3	0.961	>0.05	1.01
S	9179 ± 732	8101 ± 228	0.202	>0.05	0.88
Sb	0.193 ± 0.044	0.080 ± 0.033	0.055	**<0.05**	0.41
Sc	0.0245 ± 0.0047	0.0308 ± 0.0081	0.541	>0.05	1.26
Se	1.13 ± 0.08	1.07 ± 0.15	0.751	>0.05	0.95
Si	162 ± 34	104 ± 18	0.171	>0.05	0.64
Sm	0.00161 ± 0.00056	0.00110 ± 0.00038	0.467	>0.05	0.68
Sn	0.073 ± 0.017	0.170 ± 0.070	0.259	>0.05	2.33
Sr	3.95 ± 0.76	3.63 ± 0.84	0.786	>0.05	0.92
Tb	0.000161 ± 0.000030	0.000175 ± 0.000048	0.819	>0.05	1.09
Th	0.00180 ± 0.00034	0.00180 ± 0.00079	0.999	>0.05	1.00
Ti[a]	1.63 ± 0.24	1.35 ± 0.38	0.557	>0.05	0.83
Tl	0.00260 ± 0.00089	0.00115 ± 0.00020	0.167	>0.05	0.44
Tm	0.000157 ± 0.000025	0.000140 ± 0.000044	0.748	>0.05	0.89
U	0.0029 ± 0.0014	0.00077 ± 0.00017	0.196	>0.05	0.27
Y	0.0075 ± 0.0015	0.0063 ± 0.0020	0.648	>0.05	0.84
Yb	0.00087 ± 0.00026	0.00075 ± 0.00034	0.786	>0.05	0.86
Zn	1107 ± 93	1152 ± 161	0.814	>0.05	1.04
Zr	0.117 ± 0.059	0.053 ± 0.023	0.346	>0.05	0.45

BPH, benign prostatic hyperplasia; M, arithmetic mean; SEM, standard error of mean; t-test, Student's t-test; U-test, Wilcoxon-Mann-Whitney U-test; Bold represents significant differences.

[a] Titanium tools were used.

Table 7 Intercorrelations of selected pairs of the trace element mass fractions in normal prostate glands of adults (*r*—coefficient of correlation).

Pairs	Bi	Cr	Cs	Hg	K	Mo	Pb	Sb	Se	Sn	Zn
Ag	−0.19	−0.27	−0.16	0.32	0.14	0.13	0.15	0.22	−0.19	**0.45**	0.10
Al	−0.09	−0.04	−0.29	−0.09	0.23	−0.04	−0.13	0.04	−0.03	−0.11	−0.13
Au	−0.18	0.26	0.11	0.15	−0.27	0.34	−0.04	0.33	0.34	0.18	−0.17
B	0.10	0.02	−0.05	0.09	0.02	0.43	0.20	−0.09	−0.12	0.13	−0.15
Ba	0.14	−0.24	−0.27	0.01	−0.09	−0.16	−0.04	−0.28	−0.27	−0.05	0.19
Be	−0.19	0.25	−0.01	0.02	−0.06	0.08	0.01	−0.04	0.19	0.11	0.17
Bi	1.00	−0.26	0.16	−0.15	0.12	−0.23	0.23	−0.28	0.00	0.05	−0.07
Br	−0.44	0.03	−0.33	0.09	−0.31	0.38	0.13	0.01	−0.29	0.20	−0.17
Ca	0.16	−0.25	−0.20	−0.17	−0.22	0.06	0.07	−0.13	−0.21	0.20	−0.04
Cd	0.09	0.28	−0.24	0.03	−0.13	−0.01	0.26	−0.10	−0.10	−0.04	−0.27
Ce	**0.65**	−0.10	0.10	−0.06	0.13	−0.26	0.01	−0.22	−0.05	−0.09	−0.19
Co	0.14	0.12	−0.21	0.01	−0.21	−0.11	−0.01	0.18	−0.07	0.00	−0.09
Cr	−0.26	1.00	0.34	0.06	−0.13	0.16	−0.07	0.26	0.42	−0.21	0.03
Cs	0.16	0.34	1.00	0.27	0.21	0.17	0.27	0.07	0.32	0.08	0.15
Cu	−0.31	0.16	0.14	**0.56**	−0.10	0.39	0.14	−0.18	0.17	0.17	0.38
Dy	−0.03	−0.15	−0.31	−0.19	0.21	−0.26	−0.34	−0.11	−0.13	−0.21	−0.18
Er	−0.06	−0.09	−0.32	−0.26	0.33	−0.27	−0.32	0.01	−0.08	−0.14	−0.18
Fe	−0.13	0.42	0.04	0.09	−0.04	0.13	−0.04	0.29	0.28	−0.09	0.08
Gd	0.24	−0.15	−0.21	−0.22	0.32	−0.38	−0.24	−0.09	−0.11	−0.19	−0.23
Hg	−0.15	−0.06	0.27	1.00	0.12	0.29	0.36	0.08	0.41	0.19	0.38
Ho	−0.05	−0.08	−0.27	−0.20	0.38	−0.17	−0.31	0.02	−0.06	−0.18	−0.24
K	0.12	−0.13	0.21	0.12	1.00	−0.32	−0.18	−0.25	0.28	−0.34	0.02
La	0.03	−0.22	0.03	−0.22	0.12	−0.13	−0.07	0.04	−0.16	0.19	−0.08
Li	−0.02	0.31	0.09	−0.01	−0.20	0.31	0.26	0.25	0.19	0.33	−0.14
Mg	0.03	−0.01	0.26	0.15	0.20	−0.18	0.10	0.37	0.16	−0.30	**0.57**
Mn	−0.14	0.05	0.01	0.02	0.10	0.20	0.05	0.28	0.08	−0.02	−0.08
Mo	−0.23	0.16	0.17	0.29	−0.32	1.00	0.15	0.32	−0.14	**0.61**	−0.05
Na	−0.08	0.24	0.31	−0.01	0.23	−0.36	−0.14	0.30	0.12	−0.28	0.25
Nb	−0.18	−0.02	−0.23	0.34	−0.44	**0.56**	0.05	0.39	−0.22	**0.45**	−0.32
Nd	**0.60**	−0.13	0.01	−0.16	0.19	−0.34	−0.17	−0.16	−0.06	−0.12	−0.22
Ni	−0.21	−0.15	−0.06	**0.45**	−0.28	**0.57**	0.39	−0.12	−0.16	0.05	0.07
P	0.04	0.05	0.01	0.37	0.21	−0.03	−0.05	−0.22	0.35	−0.02	**0.80**
Pb	0.23	−0.07	0.27	0.36	−0.18	0.15	1.00	0.09	−0.05	0.36	−0.01
Pr	**0.65**	−0.12	0.06	−0.08	0.16	−0.28	−0.03	−0.21	−0.05	−0.10	−0.19
Rb	0.10	0.40	**0.58**	0.42	**0.51**	0.03	0.19	0.34	0.35	−0.15	0.27
S	−0.16	0.27	0.16	−0.02	**0.68**	−0.28	−0.25	−0.09	0.43	−0.40	0.08
Sb	−0.28	0.26	0.07	0.08	−0.25	0.32	0.09	1.00	−0.08	0.17	−0.09
Sc	**0.59**	0.01	0.36	**0.52**	0.22	−0.18	0.14	0.03	**0.63**	−0.34	**0.63**
Se	−0.01	0.42	0.32	0.41	0.28	−0.14	−0.05	−0.08	1.00	−0.13	0.28
Si	0.42	−0.05	−0.02	−0.01	0.32	−0.23	−0.11	−0.15	0.12	−0.14	−0.17
Sm	0.43	−0.14	−0.07	−0.13	0.24	−0.27	−0.11	−0.08	−0.05	−0.16	−0.21
Sn	0.05	−0.21	0.08	0.19	−0.34	**0.61**	0.36	0.17	−0.13	1.00	−0.11
Sr	0.39	−0.01	0.09	−0.22	**−0.45**	0.15	0.18	−0.12	−0.05	0.24	−0.22
Tb	0.15	−0.19	−0.29	−0.23	0.28	−0.35	−0.33	−0.06	−0.06	−0.14	−0.22
Th	**0.53**	0.01	0.04	−0.20	−0.01	−0.35	−0.12	−0.19	0.04	−0.17	−0.16
Ti[a]	−0.01	0.06	−0.04	0.03	−0.02	0.16	−0.22	−0.24	−0.12	−0.05	0.17
Tl	−0.20	0.34	0.22	0.34	**0.46**	−0.25	−0.05	−0.16	**0.64**	−0.28	**0.50**
Tm	−0.14	−0.11	−0.28	−0.11	0.40	−0.23	−0.21	0.04	−0.10	−0.19	−0.21
U	−0.10	0.07	**0.45**	−0.01	−0.11	**0.56**	0.01	0.15	−0.29	0.40	0.00
Y	−0.03	−0.29	−0.15	0.01	0.04	−0.17	0.21	0.09	−0.21	0.37	−0.04
Yb	−0.08	−0.11	−0.35	−0.25	0.34	−0.30	−0.38	−0.03	−0.10	−0.17	−0.20
Zn	−0.07	0.03	0.15	0.38	0.02	−0.05	−0.01	−0.09	0.28	−0.11	1.00
Zr	−0.19	0.10	−0.13	−0.16	0.23	−0.33	−0.31	−0.17	0.09	−0.31	−0.07

Bold represents significant differences.

[a] Titanium tools were used.

Table 8 Intercorrelations of selected pairs of the trace element mass fractions in BPH prostate gland (*r*—coefficient of correlation).

Pairs	Bi	Cr	Cs	Hg	K	Mo	Pb	Sb	Se	Sn	Zn
Ag	−0.37	0.09	−0.02	**0.49**	−0.01	0.12	0.34	−0.15	−0.46	0.13	**0.72**
Al	0.23	0.51	0.45	**0.62**	**0.70**	−0.03	**0.60**	0.42	**0.70**	−0.16	0.27
Au	−0.10	0.07	0.18	0.31	−0.02	0.10	0.13	−0.09	0.12	−0.19	0.06
B	0.40	0.09	−0.48	−0.16	−0.39	0.26	0.02	−0.37	−0.10	−0.22	−0.42
Ba	−0.22	0.29	0.42	**0.79**	**0.58**	−0.08	0.39	0.16	−0.11	0.04	**0.57**
Be	−0.05	0.37	0.18	**0.53**	0.18	0.09	**0.55**	−0.02	0.05	−0.06	0.33
Bi	1.00	0.13	0.09	0.02	0.25	0.15	−0.15	0,42	0.34	**−0.56**	−0.43
Br	−0.33	−0.18	−0.14	−0.39	−0.20	**−0.50**	0.37	−0.14	−0.22	**0.85**	−0.05
Ca	**−0.50**	**0.63**	−0.04	0.47	0.01	0.17	0.07	−0.35	0.29	0.05	0.46
Cd	0.36	**0.59**	−0.22	0.42	−0.09	0.25	−0.21	−0.16	0.26	−0.22	0.41
Ce	0.04	0.38	**0.67**	**0.81**	**0.77**	−0.11	**0.66**	0.48	0.41	−0.15	0.31
Co	0.34	0.35	0.44	0.48	0.38	-.0.21	0.31	0.33	0.37	−0.19	0.33
Cr	0.13	1.00	−0.31	0.40	0.01	**0.74**	−0.15	−0.23	**0.49**	−0.44	0.29
Cs	0.09	−0.31	1.00	0.47	**0.84**	**−0.54**	**0.56**	**0.88**	0.36	−0.12	−0.10
Cu	0.19	**0.64**	−0.21	**0.50**	0.01	0.29	−0.24	−0.22	0.36	−0.08	**0.63**
Dy	−0.02	**0.66**	0.02	0.35	0.28	0.09	0.44	−0.02	0.53	0.06	0.31
Er	0.04	**0.58**	0.26	0.44	**0.58**	0.15	0.39	0.15	0.47	−0.15	0.10
Fe	0.27	0.06	−0.34	0.27	−0.23	−0.06	−0.34	−0.16	−0.31	0.12	−0.29
Gd	−0.22	0.26	0.23	0.35	0.14	−0.13	**0.79**	0.16	0.41	0.34	0.36
Hg	0.02	0.40	0.47	1.00	**0.54**	0.18	0.43	0.26	−0.13	−0.23	**0.56**
Ho	0.04	**0.75**	−0.18	0.35	0,16	0.30	0.30	−0.18	0.27	0.01	0.45
K	0.25	0.01	**0.84**	**0.54**	1.00	−0.33	0.39	**0.75**	0.40	−0.26	−0.13
La	**0.49**	0.06	0.01	0.02	0.14	0.08	0.36	0.06	−0.01	−0.23	−0.32
Li	0.28	0.08	**0.56**	0.32	**0.59**	−0.02	0.16	**0.65**	0.24	−0.23	−0.14
Mg	−0.12	0.33	**0.56**	**0.57**	**0.55**	−0.19	0.40	0.38	**0.73**	−0.01	0.20
Mn	−0.19	−0.10	0.20	0.48	0.06	0.01	0.55	0.06	**−0.56**	0.23	0.44
Mo	0.15	**0.74**	**−0.54**	0.18	−0.33	1.00	−0.42	**−0.52**	−0.16	**−0.56**	0.14
Na	0.18	−0.28	0.35	0.16	0.26	−0.14	0.06	0.30	0.16	0.04	−0.21
Nb	−0.30	0.40	0.06	0.11	0.39	0.03	−0.08	−0.14	0.25	−0.15	0.02
Nd	0.07	0.42	**0.58**	**0.82**	**0.73**	0.04	**0.68**	0.42	0.29	−0.14	0.31
Ni	−0.38	0.46	−0.11	0.03	0.12	0.30	−0.28	−0.31	0.05	−0.30	−0.04
P	0.27	−0.29	**0.83**	0.48	**0.75**	−0.33	**0.55**	**0.77**	0.01	−0.16	−0.17
Pb	−0.15	−0.15	**0.56**	0.43	0.39	0.42	1.00	0.45	0.12	0.44	0.31
Pr	0.07	0.27	**0.64**	**0.67**	**0.74**	−0.09	**0.75**	**0.53**	0.33	−0.08	0.19
Rb	0.09	0.13	0.29	0.12	0.35	0.20	0.26	0.19	0.07	−0.39	0.16
S	0.31	−0.30	**0.93**	0.41	**0.85**	−0.43	**0.58**	**0.92**	0.31	−0.18	−0.28
Sb	0.42	0.23	**0.88**	0.26	**0.75**	**−0.52**	0.45	1.00	0.15	−0.21	−0.11
Sc	**−0.82**	**0.50**	−0.48	**0.64**	−0.32	0.12	0.05	−0.08	−0.29	**0.53**	**0.77**
Se	0.34	**0.49**	0.36	−0.13	0.40	−0.16	0.12	0.15	1.00	−0.31	−0.28
Si	0.21	−0.05	**0.89**	0.40	**0.92**	−0.40	**0.49**	**0.83**	**0.57**	−0.25	−0.24
Sm	0.06	0.70	0.21	**0.65**	0.41	0.02	0.20	0.11	**0.61**	−0.14	0.48
Sn	**−0.56**	−0.44	−0.12	−0.23	−0.26	**−0.56**	0.44	−0.21	−0.31	1.00	0.26
Sr	−0.04	0.45	0.34	−0.05	**0.52**	−0.16	−0.07	−0.08	**0.50**	−0.07	−0.22
Tb	0.09	0.25	0.33	**0.53**	**0.59**	0.16	0.16	0.25	0.05	−0.07	0.10
Th	−0.17	0.26	0.43	0.44	0.43	−0.33	0.77	0.33	**0.52**	0.27	0.35
Ti[a]	−0.23	**0.49**	−0.36	0.21	−0.33	0.26	0.18	**−0.52**	−0.08	0.05	0.45
Tl	**0.66**	0.03	−0.18	−0.17	0.03	0.09	0.11	0.02	−0.13	−0.14	−0.46
Tm	−0.08	**0.71**	−0.06	0.44	0.20	0.23	0.46	−0.17	0.35	0.05	0.43
U	0.37	−0.08	**0.86**	**0.58**	**0.86**	−0.28	**0.54**	**0.82**	0.32	−0.23	−0.17
Y	0.05	**0.74**	0.05	0.43	0.42	0.23	0.29	−0.04	0.46	−0.13	0.22
Yb	−0.11	**0.62**	0.01	0.25	0.33	0.03	0.30	−0.10	**0.50**	0.07	0.21
Zn	−0.43	0.29	−0.10	**0.57**	−0.13	0.14	0.31	−0.11	−0.28	0.26	1.00
Zr	−0.20	0.08	0.01	0.17	−0.18	0.13	0.16	−0.26	0.02	−0.07	0.09

BPH, benign prostatic hyperplasia; Bold represents significant differences.
[a] Titanium tools were used.

reported minimal results [21,24,26,31]. No published data referring to Ag, Al, Au, B, Ba, Be, Bi, Ce, Cs, Dy, Er, Gd, Hg, Ho, La, Li, Mo, Nb, Nd, Pr, Sb, Sc, Si, Sm, Sn, Tb, Th, Tl, Tm, U, Y, Yb, and Zrmass fractions in BPH gland were found.

In previous publications [15–17], it was shown that in the histologically normal prostates of males in the sixth to ninth decades, the magnitude of mass fractions of all chemical elements were maintained at near constant levels. No age-related differences in mass fraction of chemical elements in the hyperplastic prostate glands of men aged from 38 to 83 years were found in this study (Table 5). The only exclusion was the mass fraction of Cr, Sc, and Sn. The mean mass fractions of Cr, Sc, and Sn in the hyperplastic prostate glands of males aged 66–83 years were 1.44, 1.95, and 2.83 times higher than in the hyperplastic prostate glands of males aged 38–65 years, respectively.

No differences in mass fraction of chemical elements in prostate of two BPH patient groups with different stage of disease and similar age ranges were found (Table 6). The only exclusion was the mass fraction of Hg and Sb. The mean mass fractions of Hg and Sb in the prostate glands of BPH patient with stage 1–2 of disease were 1.63, and 2.41 times higher than in the prostate of patient with stage 3 of disease. The biochemical reason behind the decrease of Hg and Sb mass fractions in the stage 3 of BPH requires further study for a more complete understanding.

In control group of males a statistically significant direct correlation was found, for example, between the prostatic Zn and Mg ($r = 0.57$), Zn and P ($r = 0.80$), Zn and Sc ($r = 0.63$), and Zn and Tl ($r = 0.50$) (Table 7). In hyperplastic prostates some correlations between trace elements found in the control group were no longer evident, for example, correlations for some pairs with Zn (Zn–Mg and Zn–P), but other correlations (direct Zn–Ag, Zn–Ba, Zn–Cu, and Zn–Hg) were arisen (Table 8). Thus, accepting the levels and relationships of chemical 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 chemical elements mass fractions in BPH gland were found.

Numerous *in vitro* and *in vivo* studies have evidenced that the disturbed homeostasis of Ca, Zn, Fe, and Se can play a very important role in the mechanism of uncontrolled cellular hyperplasia [13,56,57]. The high level of Ca, Zn, Fe, Se and some other chemical 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 in 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 Ca, Zn, Fe, Se and some other chemical elements deficiencies [12,58–61], 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]. This study data reveal that there are no any differences between Ca, Zn, and Fe mass fractions in the prostate of healthy individuals and patients with BPH. Moreover, the mean level of Se content in hyperplastic prostates is significantly higher than 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.

5. Conclusion

This work revealed that there is a significant tendency for an increase in Bi, Cr, Hg, K, Sb, and Se mass fraction in hyperplastic prostates. Present study finding of chemical element contents and correlation between pairs of chemical 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 chemical elements but also a great disturbance in the relationships of 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 Ca, 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 Ca, Zn, Fe, and Se supplementations on BPH prevention and treatment. An estimation of the significance of prostatic chemical element levels as the BPH markers is planned in the future investigations.

The current study had sufficient sample size to detect the differences between the prostatic levels of 66 chemical elements in patients with BPH and healthy male. A similarly but more larger future study is needed to explore possible chemical element variations in normal and BPH prostate due to peculiarity of diet and cacoethes, such as smoking, alcohol ingestion, *etc*.

Author contributions

Study concept and design: Vladimir Zaichick.
Data acquisition: Vladimir Zaichick.
Drafting of manuscript: Sofia Zaichick.
Critical revision of the manuscript: Sofia Zaichick.
Final approval of manuscript: Vladimir Zaichick.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The authors are grateful to Dr. T. Sviridova, Medical Radiological Research Center, Obninsk, and Prof. A.A. Zhavoronkov, Institute of Human Morphology, Russian Academy of Medical Sciences, Moscow, for supplying prostate samples. The authors are also grateful to Dr. V. Karandaschev, Dr. S. Nosenko, and I. Moskvina, Institute of Microelectronics

Technology and High Purity Materials, Chernogolovka, Russia, for their help in ICP-AES and ICP-MS analysis.

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