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The Variation with Age of 67 Macro- and Microelement Contents in Nonhyperplastic Prostate Glands of Adult and Elderly Males Investigated by Nuclear Analytical and Related Methods

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Abstract To clarify age-related changes of 67 macro- and microelement contents in prostate gland of adult and geriatric males, a quantitative measurement by five analytical methods was performed. The nonhyperplastic prostate glands of 65 subjects (European-Caucasian aged 21–87 years) were investigated by 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 prostates were obtained at autopsy from subjects who died from acute illness (cardiac insufficiency, stroke, embolism of pulmonary artery, alcohol poisoning) and trauma. None of the subjects had any symptoms of prostatic disease, and all prostates were classified as histologically normal. The combination of nuclear (EDXRF, INAA-SLR, and INAA-LLR) and inductively coupled plasma (ICP-AES and ICP-MS) analytical methods allowed estimation of the contents of 67 chemical elements and precisely determined the mass fraction of 54 elements in the tissue samples of nonhyperplastic adult and geriatric prostate glands. This work's results reveal that there is a significant increase with age of Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, Th, U, and Zn mass fractions in the prostate tissue of healthy individuals of ages from 21 to 60 years, as well as an increase in Ba from age 61 up to 87 years. It implies that an age-related increase and excess in Ba, Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, Th, U, and Zn mass fraction in prostatic tissue may be one of the main factors in the etiology of benign prostatic hyperplasia (BPH) and prostate carcinoma (PCa).

This study is dedicated to the blessed memory of my good friend Professor Dr. Robert E. Jervis (University of Toronto), who was a Canadian pioneer in nuclear chemistry and application of nuclear analytical methods in the life sciences.

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Keywords Chemical elements · Nonhyperplastic adult and geriatric prostate gland · EDXRF · INAA · ICP-AES · ICP-MS · Age-related changes

Introduction

The human prostate gland is the only internal organ that continues to enlarge throughout adulthood [1, 2]. The prevalence of benign enlargement of the prostate (benign prostatic hyperplasia—BPH) and prostate carcinoma (PCa) rises sharply with age. For example, the prevalence of PCa is approximately three orders of magnitude higher for males older than 40 years, compared with younger males. To date, we have no precise knowledge of the biochemical processes underlying the etiology and pathogenesis of BPH and PCa. There are a few hypotheses on the subject [3–11]. Among these hypotheses, the possible role of the oxidative stress, which increased with age, has been noted in the literature [7, 8].

Reactive oxygen species (ROS) are widely considered to be a causal factor not only in aging but in a number of pathological conditions, including abnormal cell proliferation and carcinogenesis. Aging, considered as an impairment of body functions over time, caused by the accumulation of molecular damage in deoxyribonucleic acid (DNA), proteins and lipids, is also characterized by an increase in intracellular oxidative stress due to the monotonic decrease of intracellular ROS scavenging with age [7]. Oxidative damage to cellular macromolecules which induce cancer can also arise through overproduction of ROS and faulty antioxidant and/or DNA repair mechanisms [12]. Overproduction of ROS is associated with inflammation, radiation, and other factors, including overload of some chemical elements, in both blood and certain tissues, or deficiency in chemical elements with antioxidant properties [13–19]. Studies have shown that the imbalance in the composition of chemical elements may cause different types of pathology. The importance of appropriate levels of many chemical elements is indisputable, due to their beneficial roles when in specific concentration ranges; while on the other hand, they can cause toxic effects with excessively high or low concentrations [16].

About 50 years ago, a postulate of trace element homeostasis in human body tissues and fluids in normal environmental and health conditions was formulated [16]. It was supposed that the homeostatic levels of chemical elements depend on many factors such as gender, age, race, diet, unhealthy lifestyle habits, climate, biogeochemical and environmental characteristics of habitation, occupational exposure to certain chemical compounds, and so on [16]. It was also supposed that all chemical elements are actively or inactively involved in normal metabolism of human body tissues and fluids and that a deficiency, or an excess, of some of them, as well as an imbalance of chemical element contents, could be a causative factor for many diseases, including cancer [16].

In our previous studies, high mass fractions of Al, Au, B, Ba, Br, Ca, Cl, Cr, Ga, Li, Mg, Na, Ni, Sr, U, and Zn were observed in nonhyperplastic prostate tissues of adult males, when compared with levels in nonprostatic soft tissues of the human body [20–23]. Moreover, it was shown that the levels of Zn and some other chemical elements in prostate tissue are androgen-dependent parameters [24–29]. The mass fractions of these elements in prostate tissue jump up during puberty and continue to increase in young adult males. However, some questions about the age dependence of chemical element mass fraction in prostate glands of adult and, particularly, elderly males (≥61 years old) still remain unanswered.

The main epidemiologic associative factor of BPH and PCa is age, and the prevalence of these diseases increases dramatically after 40 years. One valuable way to elucidate the situation is to compare the prostatic mass fractions of chemical elements in young adult (the norm) with those in older adult and geriatric prostate. Carcinogenesis is considered to have four stages: initiation, promotion, progression, and metastasis. Thus, the findings of the excess or deficiency of prostatic chemical element contents and the perturbations of their relative proportions in nonhyperplastic prostate glands of adult and elderly males may give an indication of their role in at least two stages of carcinogenesis: initiation and promotion.

The data available on chemical element mass fractions in geriatric nonhyperplastic prostate is extremely limited [30–32]. There are many studies regarding chemical element content in prostate of adult males, using chemical techniques and instrumental methods [33–59]. However, 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 many hours. There is evidence that certain quantities of chemical elements are lost as a result of such treatment [60, 61]. Moreover, only a few of these studies employed quality control using certified reference materials (CRM) for determination of the chemical element mass fractions.

We define three age groups for prostates in our study; groups 1 (from young adults aged 21 to 40 years), 2 (from adults aged 41 to 60 years), and 3 (from elderly adults aged 61 to 87 years). The primary purpose of this study was to determine reliable values for chemical element mass fractions in the nonhyperplastic prostate of subjects of different age from young adult to elderly persons using five analytical methods: an energy dispersive X-ray fluorescence (EDXRF), an instrumental neutron activation analysis with high resolution spectrometry of short-lived (INAA-SLR) and long-lived (INAA-LLR) radionuclides, an inductively coupled plasma atomic emission spectrometry (ICP-AES), and an inductively coupled plasma mass spectrometry (ICP-MS). The second aim was to compare the chemical element mass fractions in prostate glands of our age group 1 with those of group 2 and 3. The final aim was to compare the results of this study with reference data for nonhyperplastic prostate gland of adult males of all ages.

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

Materials and Methods

Samples of the human prostate were obtained from randomly selected autopsy specimens of 65 males (European-Caucasian) aged 21 to 87 years. All samples were obtained within 24 h after death. Age ranges for subjects were divided into the three age groups defined above, with group 1 (30.4±1.1 years, M±SEM, n=28), group 2 (49.6±1.1 years, M±SEM, n=27), and group 3 (68.8±2.7 years, M±SEM, n=10). These groups were selected to reflect the condition of prostate of young adult, mid-adult, and elderly adult. 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, metabolism, or its trace element content. The typical causes of death of most of these patients included acute illness (cardiac insufficiency, stroke, embolism of pulmonary artery, alcohol poisoning) and trauma. All prostate glands were 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 content determination. Only the posterior part of the prostate, including the transitional, central, and peripheral zones, was investigated. 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 100 mg was used for chemical element measurement by instrumental NAA-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 50 mg was used for chemical element measurement by instrumental NAA-LLR. The samples for INAA-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 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) 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., 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 of 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 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 [20–23, 25].

The mass fractions of Br, Fe, Rb, Sr, and Zn were measured by EDXRF; the mass fractions of Br, Ca, Cl, 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, 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, gamma-energies, wavelength, isotopes, spectrometers, spectrometer parameters, and operating conditions were presented in our earlier publications concerning the chemical elements of human prostate gland [20–23, 25].

A dedicated computer program of INAA mode optimization was used [62]. Using the Microsoft Office Excel program to provide a summary of statistical results, the arithmetic mean, standard deviation, standard error of mean, minimum and maximum values, median, and 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 reliability of difference in the results between two age groups of different group pairs was evaluated by Student's parametric *t* test. For the construction of "chemical element mass fraction versus age" diagrams, the Microsoft Office Excel program was also used.

Results

Table 1 depicts the results obtained for 67 elemental mass fractions (arithmetic mean±standard deviation, possible upper limit of the mean, detection limit) in nonhyperplastic prostate glands of males in the age range 21–87 years measured by means of the five analytical methods described above. 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 collected. The possible upper limit of the mean ($\leq M$) 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:

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

where C_i is the individual value of chemical element mass fraction in the ith 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 investigated samples. Generally, the mass fractions of Rh and Te were lower than the

Table 1 Arithmetic means (M±SD) or possible upper limits of the means (≤*M*) of elemental mass fractions (mg/kg, dry mass basis) in nonhyperplastic prostate glands of males of ages 21–87 years (*n*=65) obtained by means of five analytical methods

Element	EDXRF	NAA-SLR	NAA-LLR	ICP-AES	ICP-MS	Derived value
Ag	–	–	0.055±0.047	–	0.039±0.032	0.047±0.036
Al	–	–	–	33±18	33±18	33±18
As	–	–	<0.1 (DL)	–	≤0.018	≤0.018
Au	–	–	<0.01 (DL)	–	0.0042±0.0037	0.0042±0.0037
B	–	–	–	0.94±0.70	0.94±0.70	0.94±0.70
Ba	–	–	<100 (DL)	1.34±0.89	–	1.34±0.89
Be	–	–	–	–	0.00093±0.00032	0.00093±0.00032
Bi	–	–	–	–	0.020±0.046	0.020±0.046
Br	37±31	33±23	–	–	27±19	34±23
Ca	–	2150±802	–	2272±1052	–	2285±1066
Cd	–	–	<2 (DL)	–	0.91±0.59	0.91±0.59
Ce	–	–	<0.1 (DL)	–	0.027±0.022	0.027±0.022
Cl	–	12,791±3206	–	–	–	12,791±3206
Co	–	–	0.038±0.022	–	0.037±0.027	0.039±0.028
Cr	–	–	0.47±0.37	–	0.53±0.38	0.52±0.42
Cs	–	–	<0.05 (DL)	–	0.034±0.015	0.034±0.015
Cu	–	–	–	10.3±4.9	–	10.3±4.9
Dy	–	–	–	–	0.0027±0.0023	0.0027±0.0023
Er	–	–	–	–	0.0015±0.0013	0.0015±0.0013
Eu	–	–	<0.001 (DL)	–	≤0.00054	≤0.00054
Fe	107±39	–	99±47	123±40	–	111±34
Ga	–	–	–	–	≤0.081	≤0.081
Gd	–	–	<0.02 (DL)	–	0.0026±0.0021	0.0026±0.0021
Hf	–	–	<0.2 (DL)	–	≤0.018	≤0.018
Hg	–	–	0.044±0.044	–	0.046±0.042	0.044±0.036
Ho	–	–	–	–	0.00053±0.00043	0.00053±0.00043
Ir	–	–	–	–	≤0.00042	≤0.00042
K	–	11,896±2490	–	12,537±2521	–	12,206±2591
La	–	–	<0.5 (DL)	–	0.073±0.092	0.073±0.092
Li	–	–	–	0.041±0.026	0.041±0.026	0.041±0.026
Lu	–	–	<0.003 (DL)	–	≤0.00022	≤0.00022
Mg	–	1149±484	–	1052±412	–	1115±472
Mn	–	1.41±0.44	–	1.38±0.35	1.38±0.35	1.42±0.45
Mo	–	–	–	–	0.28±0.17	0.28±0.17
Na	–	10,886±2491	–	10,768±2168	–	10,790±2380
Nb	–	–	–	–	0.0047±0.0051	0.0047±0.0051
Nd	–	–	<0.1 (DL)	–	0.0122±0.0095	0.0122±0.0095
Ni	–	–	–	–	3.5±2.3	3.5±2.3
P	–	–	–	7679±1710	–	7679±1710
Pb	–	–	–	–	1.9±2.5	1.9±2.5
Pd	–	–	–	–	≤0.0074	≤0.0074
Pr	–	–	–	–	0.0031±0.0025	0.0031±0.0025
Pt	–	–	–	–	≤0.00059	≤0.00059
Rb	17.0±6.4	–	12.3±4.7	–	15.7±4.7	14.9±4.6
Re	–	–	–	–	≤0.00100	≤0.00100
Rh	–	–	–	–	<0.01 (DL)	<0.01 (DL)
S	–	–	–	8750±1098	–	8750±1098
Sb	–	–	0.049±0.036	–	0.034±0.028	0.043±0.034

Table 1 (continued)

Element	EDXRF	NAA-SLR	NAA-LLR	ICP-AES	ICP-MS	Derived value
Sc	–	–	0.021±0.020	–	–	0.021±0.020
Se	–	–	0.65±0.23	–	0.78±0.26	0.72±0.25
Si	–	–	–	104±60	–	104±60
Sm	–	–	<0.01 (DL)	–	0.0024±0.0019	0.0024±0.0019
Sn	–	–	–	–	0.25±0.28	0.25±0.28
Sr	2.051.88	–	–	1.97±1.71	–	2.03±1.80
Ta	–	–	<0.01 (DL)	–	≤0.0053	≤0.0053
Tb	–	–	<0.03 (DL)	–	0.00035±0.00031	0.00035±0.00031
Te	–	–	–	–	<0.003 (DL)	<0.003 (DL)
Th	–	–	<0.05 (DL)	–	0.0026±0.0030	0.0026±0.0030
Ti[a]	–	–	–	–	2.4±2.7	2.4±2.7
Tl	–	–	–	–	0.00139±0.00064	0.00139±0.00064
Tm	–	–	–	–	0.00024±0.00020	0.00024±0.00020
U	–	–	<0.07 (DL)	–	0.0052±0.0088	0.0052±0.0088
V	–	–	–	≤0.22	–	≤0.22
Y	–	–	–	–	0.017±0.019	0.036±0.054
Yb	–	–	<0.03 (DL)	–	0.0014±0.0013	0.0037±0.0062
Zn	928±628	–	795±573	844±759	844±759	856±634
Zr	–	–	<0.3 (DL)	–	0.040±0.046	0.040±0.046

The mean of all results was used

M arithmetic mean, *SD* standard deviation, ≤*M* possible upper limit of the mean value, *DL* detection limit, *EDXRF* energy dispersive X-ray fluorescence, *NAA-SLR* neutron activation analysis with high resolution spectrometry of short-lived radionuclides, *NAA-LLR* neutron activation analysis with high resolution spectrometry of long-lived radionuclides, *ICP-AES* inductively coupled plasma atomic emission spectrometry, *ICP-MS* inductively coupled plasma mass spectrometry, *Derived value* for elements investigated by two or more methods

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

corresponding DL (in mg/kg on a dry mass basis) <0.01 and <0.003, respectively.

To analyze the effect of age on the chemical element mass fractions in the prostate glands, we examined the three age groups, described above. Tables 2, 3, 4, and 5 present basic statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, and percentiles with 0.025 and 0.975 levels) of the Ag, Al, Au, B, Ba, Be, Bi, Br, Ca, Cd, Ce, Cl, Co, Cr, Cs, Cu, Dy, Er, Fe, Gd, Hg, Ho, K, La, Li, Mg, Mn, Mo, Na, Nb, Nd, Ni, P, Pb, Pr, Rb, S, Sb, Sc, Se, Si, Sm, Sn, Sr, Tb, Th, Ti, Tl, Tm, U, Y, Yb, Zn, and Zr mass fractions (mg/kg, dry mass basis) in adult and geriatric prostate glands of males in the age range 21–40 years (group 1), 41–60 years (group 2), 61–87 years (group 3), and 41–87 years (groups 2 and 3, combined), respectively. The contents of these 54 elements were measured in all, or a major portion, of prostate tissue samples. The ratios of means and the reliability of difference between mean values of chemical element mass fraction in two age groups of the different group pairs are presented in Table 6.

Figure 1 shows individual data set for the Ba, Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, Th, U, and Zn mass fraction in the nonhyperplastic prostate gland of males aged between 21 and 87 years and their trend lines with equations of best fit. In our study, the best fit in the proportion variance accounted for (i.e., R^2) sense maximizes the value of R^2 using a linear, exponential, logarithmic, power, or polynomial law.

To compare our results with published data for the chemical element mass fractions in the prostate gland of adults, we examined all our prostate data of males aged 21–87 years. The comparison of our results with published data for the 67 chemical element mass fractions (mg/kg, dry mass basis) in the prostate of adult males is shown in Table 7. Because some values for chemical element mass fractions were not expressed on a dry mass basis in other's publications, we recalculated these values using published data for water—83 % [63] and ash—1.0 % [64] contents in the prostate of adult men.

Discussion

The use of five analytical methods allowed us to estimate the mass fractions of 67 elements in nonhyperplastic adult and geriatric prostate glands of males in the age range 21–87 years. Good agreement (Table 1) was found between the results

Table 2 Basic statistical parameters of trace element mass fraction (mg/kg, dry mass basis) in the nonhyperplastic prostate gland of males of ages 21–40 years (the age group 1, *n*=28)

Element	M	SD	SEM	Min	Max	Median	P0.025	P0.975
Ag	0.057	0.041	0.008	0.00800	0.126	0.0650	0.00915	0.125
Al	32.0	18.6	4.5	6.80	68.2	27.7	9.76	65.6
Au	0.0042	0.0040	0.0010	0.00100	0.0149	0.0024	0.00100	0.0132
B	0.771	0.270	0.072	0.400	1.30	0.750	0.433	1.24
Ba	1.15	0.66	0.16	0.410	2.59	1.09	0.425	2.46
Be	0.000912	0.000264	0.000064	0.000700	0.00180	0.000900	0.000700	0.00152
Bi	0.00438	0.00235	0.00061	0.00180	0.0102	0.00410	0.00187	0.00912
Br	32.1	28.4	5.7	6.00	132	24.7	6.66	105
Ca	2112	813	169	952	4102	1810	1088	3543
Cd	0.595	0.315	0.076	0.230	1.27	0.530	0.230	1.20
Ce	0.0206	0.0180	0.0044	0.00500	0.0750	0.0150	0.00540	0.0630
Cl	12,036	3902	1177	4500	19,900	12,700	5575	18,500
Co	0.0306	0.0140	0.0027	0.0135	0.0758	0.0274	0.0140	0.0629
Cr	0.473	0.407	0.078	0.0470	1.90	0.331	0.0639	1.34
Cs	0.0348	0.0103	0.0025	0.0240	0.0550	0.0320	0.0244	0.0542
Cu	11.0	5.3	1.4	5.40	26.3	9.40	5.82	22.8
Dy	0.00246	0.00224	0.00054	0.000400	0.00695	0.00124	0.000512	0.00689
Er	0.00142	0.00144	0.00035	0.000160	0.00485	0.000860	0.000228	0.00443
Fe	99.1	30.6	5.9	50.0	168	99.0	55.2	163
Gd	0.00227	0.00215	0.00052	0.000300	0.00740	0.00120	0.000460	0.00680
Hg	0.0349	0.0218	0.0043	0.0132	0.100	0.0280	0.0143	0.0904
Ho	0.00047	0.00048	0.00012	0.000090	0.00164	0.000230	0.000090	0.00148
K	12,852	2761	552	6300	18,102	13,023	7980	18,031
La	0.061	0.078	0.020	0.00800	0.240	0.0155	0.00800	0.236
Li	0.0395	0.0271	0.0065	0.0150	0.0970	0.0290	0.0150	0.0910
Mg	1170	545	114	452	2400	960	545	2389
Mn	1.56	0.46	0.11	0.950	3.10	1.50	1.02	2.61
Mo	0.288	0.139	0.034	0.110	0.580	0.260	0.118	0.580
Na	10,564	2639	518	4900	15,622	10,306	5769	15,171
Nb	0.00365	0.00381	0.00092	0.00100	0.0150	0.00200	0.00100	0.0122
Nd	0.0102	0.0086	0.0021	0.00300	0.0320	0.00600	0.00340	0.0284
Ni	3.97	2.06	0.50	0.200	9.20	3.70	0.800	8.24
P	7771	1549	376	5307	10,729	7821	5473	10,546
Pb	1.06	1.43	0.35	0.250	5.40	0.480	0.274	4.73
Pr	0.00255	0.00229	0.00056	0.000700	0.00940	0.00160	0.000740	0.00780
Rb	15.4	3.9	0.7	7.70	24.0	15.3	8.42	22.8
S	8888	795	193	7797	10,293	8728	7799	10,218
Sb	0.0452	0.0311	0.0060	0.00900	0.157	0.0435	0.0110	0.113
Sc	0.0141	0.0131	0.0027	0.00350	0.0624	0.0110	0.00373	0.0474
Se	0.681	0.222	0.043	0.216	1.14	0.641	0.329	1.12
Si	107	67	16	39.2	258	75.9	40.7	247
Sm	0.00203	0.00200	0.00048	0.000500	0.00660	0.00120	0.000500	0.00616
Sn	0.124	0.102	0.026	0.0300	0.340	0.110	0.0300	0.325
Sr	1.41	1.31	0.33	0.600	6.05	1.01	0.649	4.61
Tb	0.000293	0.000315	0.000077	0.000070	0.00110	0.000200	0.000070	0.00102
Th	0.00163	0.00109	0.00026	0.000500	0.00400	0.00120	0.000500	0.00372
Ti[a]	1.82	2.18	0.53	0.700	8.30	0.840	0.700	7.39
Tl	0.00141	0.00053	0.00013	0.000200	0.00240	0.00130	0.000400	0.00232
Tm	0.000227	0.000237	0.000058	0.000050	0.000770	0.000120	0.000054	0.000722
U	0.00210	0.00193	0.00052	0.000540	0.00770	0.00137	0.000589	0.00652
Y	0.0162	0.0159	0.0040	0.00200	0.0510	0.00750	0.00238	0.0469
Yb	0.00131	0.00152	0.00037	0.000100	0.00430	0.000500	0.000140	0.00426
Zn	570	236	45	246	1119	552	252	1091
Zr	0.046	0.065	0.016	0.0100	0.250	0.0200	0.0100	0.214

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

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

Table 3 Basic statistical parameters of trace element mass fraction (mg/kg, dry mass basis) in the nonhyperplastic prostate gland of males of ages 41–60 years (the age group 2, *n*=27)

Element	M	SD	SEM	Min	Max	Median	P0.025	P0.975
Ag	0.0426	0.0329	0.0075	0.0100	0.155	0.0420	0.0100	0.117
Al	33.9	18.8	4.4	9.60	73.3	28.9	11.3	71.5
Au	0.00316	0.00274	0.00073	0.00100	0.0100	0.00215	0.00100	0.00912
B	1.03	0.88	0.22	0.300	3.00	0.650	0.300	2.93
Ba	1.10	0.58	0.14	0.200	2.41	1.05	0.268	2.25
Be	0.000941	0.000279	0.000067	0.000700	0.00170	0.00100	0.000700	0.00154
Bi	0.038	0.064	0.015	0.00100	0.205	0.00630	0.00121	0.201
Br	32.6	18.9	3.9	12.0	80.7	29.4	12.3	71.3
Ca	2611	1380	309	1180	6893	2242	1192	5950
Cd	1.09	0.60	0.14	0.320	2.40	1.07	0.320	2.17
Ce	0.0323	0.0263	0.0064	0.00600	0.0960	0.0220	0.00720	0.0944
Cl	13,800	2095	792	10,100	16,200	14,600	10,355	15,990
Co	0.0427	0.0233	0.0050	0.0165	0.106	0.0392	0.0168	0.101
Cr	0.502	0.394	0.086	0.0300	1.81	0.389	0.0300	1.39
Cs	0.0350	0.0176	0.0040	0.0100	0.0870	0.0300	0.0123	0.0749
Cu	10.6	4.9	1.2	4.10	22.2	8.70	4.94	20.5
Dy	0.00275	0.00213	0.00052	0.000690	0.00857	0.00202	0.000694	0.00736
Er	0.00145	0.00124	0.00030	0.000400	0.00530	0.000970	0.000432	0.00440
Fe	124	35.4	7.2	62.0	210	122	66.0	197
Gd	0.00288	0.00213	0.00052	0.000600	0.00850	0.00230	0.000680	0.00742
Hg	0.0582	0.0443	0.0092	0.00770	0.147	0.0380	0.0140	0.143
Ho	0.00058	0.00044	0.00010	0.000160	0.00179	0.000465	0.000169	0.00151
K	11,765	2413	527	6325	18,198	11,535	7177	16,263
La	0.097	0.111	0.025	0.00900	0.324	0.0400	0.00945	0.313
Li	0.0410	0.0233	0.0058	0.0170	0.100	0.0300	0.0185	0.0921
Mg	1101	443	97	447	2060	1062	526	1985
Mn	1.35	0.48	0.12	0.750	2.80	1.30	0.810	2.40
Mo	0.318	0.213	0.050	0.100	0.850	0.255	0.109	0.782
Na	10,781	2066	440	6415	14,200	11,094	6635	13,951
Nb	0.00613	0.00666	0.00162	0.00100	0.0200	0.00300	0.00100	0.0196
Nd	0.0139	0.0108	0.0027	0.00300	0.0420	0.00900	0.00338	0.0375
Ni	3.28	2.81	0.68	0.200	9.50	2.80	0.320	8.66
P	7808	2055	484	5969	14,838	7231	6040	12,645
Pb	2.53	3.09	0.71	0.260	10.7	0.790	0.265	9.76
Pr	0.00364	0.00272	0.00066	0.000600	0.0106	0.0025	0.000800	0.00976
Rb	15.1	5.3	1.1	5.90	26.5	14.3	6.14	25.8
S	8509	1362	321	5662	12,567	8555	6383	11,286
Sb	0.0442	0.0401	0.0082	0.0100	0.158	0.0312	0.0100	0.155
Sc	0.0310	0.0251	0.0061	0.00460	0.0771	0.0206	0.00628	0.0769
Se	0.722	0.211	0.044	0.318	1.22	0.754	0.339	1.09
Si	102	57	14	40.4	235	94.1	41.8	214
Sm	0.00269	0.00181	0.00043	0.000600	0.00700	0.00235	0.000643	0.00666
Sn	0.377	0.351	0.081	0.0600	1.11	0.200	0.0645	1.06
Sr	2.51	2.19	0.55	1.00	8.90	1.48	1.00	7.51
Tb	0.000392	0.000309	0.000075	0.000070	0.00120	0.000300	0.000082	0.00104
Th	0.00292	0.00395	0.00096	0.000500	0.0172	0.00150	0.000540	0.0125
Ti[a]	3.45	3.36	0.82	0.700	13.7	2.19	0.700	11.1
Tl	0.00131	0.00067	0.00015	0.000500	0.00270	0.00130	0.000540	0.00246
Tm	0.000242	0.000189	0.000046	0.000040	0.000830	0.000200	0.000056	0.000666
U	0.0077	0.0112	0.0026	0.000790	0.0381	0.00297	0.000858	0.0353
Y	0.0214	0.0246	0.0056	0.00300	0.0840	0.0100	0.00300	0.0786
Yb	0.00140	0.00131	0.00032	0.000200	0.00510	0.000700	0.000280	0.00438
Zn	1135	830	160	228	4298	1059	240	2818
Zr	0.0359	0.0272	0.0066	0.0100	0.0900	0.0300	0.0100	0.0860

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

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

Table 4 Basic statistical parameters of trace element mass fraction (mg/kg, dry mass basis) in the nonhyperplastic prostate gland of males of ages 61–87 years (the age group 3, n=10)

Element	M	SD	SEM	Min	Max	Median	P0.025	P0.975
Ag	0.0284	0.0190	0.0063	0.00500	0.0671	0.0240	0.00660	0.0635
Al	34.7	16.0	6.0	15.5	61.7	33.5	16.6	59.8
Au	0.0064	0.0042	0.0017	0.00100	0.0106	0.00730	0.00113	0.0105
B	1.07	0.85	0.32	0.300	2.80	0.900	0.300	2.58
Ba	2.35	1.28	0.48	0.620	4.33	2.61	0.703	4.17
Be	0.00094	0.00052	0.00020	0.000700	0.00210	0.000700	0.000700	0.00194
Bi	0.0080	0.0076	0.0029	0.00200	0.0197	0.00500	0.00209	0.0195
Br	34.5	11.6	4.4	21.8	54.7	34.0	22.2	52.7
Ca	1971	598	211	1317	3140	1827	1339	2999
Cd	1.19	0.78	0.29	0.470	2.39	0.900	0.479	2.35
Ce	0.0276	0.0202	0.0076	0.00600	0.0690	0.0260	0.00705	0.0630
Cl	13,206	2554	1474	11,270	16,100	12,248	11,319	15,907
Co	0.056	0.056	0.019	0.0200	0.200	0.0400	0.0206	0.172
Cr	0.74	0.53	0.20	0.285	1.60	0.500	0.301	1.57
Cs	0.0310	0.0160	0.0060	0.0200	0.0630	0.0210	0.0200	0.0594
Cu	7.7	3.3	1.3	5.70	14.3	6.35	5.76	13.4
Dy	0.0034	0.0032	0.0012	0.00102	0.0104	0.00227	0.00115	0.00930
Er	0.00154	0.00095	0.00036	0.000560	0.00341	0.00137	0.000586	0.00319
Fe	116	31	10	76.0	163	109	78.2	162
Gd	0.00294	0.00177	0.00067	0.00100	0.00650	0.00250	0.00111	0.00607
Hg	0.037	0.036	0.012	0.0200	0.130	0.0220	0.0200	0.112
Ho	0.00054	0.00029	0.00011	0.000240	0.00109	0.000450	0.000251	0.00104
K	11,347	2262	800	7792	14,223	11,023	8037	14,121
La	0.033	0.037	0.014	0.0100	0.113	0.0170	0.0100	0.103
Li	0.044	0.035	0.013	0.0150	0.101	0.0270	0.0159	0.0988
Mg	992	316	112	551	1480	922	572	1451
Mn	1.26	0.24	0.09	0.900	1.60	1.30	0.930	1.57
Mo	0.190	0.052	0.020	0.100	0.240	0.210	0.108	0.239
Na	11,552	2447	865	9132	15,300	10,635	9225	15,264
Nb	0.00371	0.00263	0.00099	0.00100	0.00800	0.00400	0.00100	0.00770
Nd	0.0130	0.0086	0.0033	0.00300	0.0300	0.0130	0.00345	0.0278
Ni	2.67	1.51	0.57	1.00	4.70	2.90	1.03	4.61
P	7124	1085	410	6049	8984	6717	6057	8848
Pb	1.98	2.21	0.83	0.150	6.10	0.870	0.158	5.70
Pr	0.00326	0.00236	0.00089	0.000800	0.00810	0.00320	0.000890	0.00740
Rb	12.8	4.1	1.4	7.80	17.9	12.0	7.88	17.8
S	9035	988	373	7966	10,565	8942	7994	10,495
Sb	0.0389	0.0258	0.0086	0.00800	0.0900	0.0380	0.00860	0.0824
Sc	0.0203	0.0108	0.0063	0.00990	0.0315	0.0194	0.0104	0.0309
Se	0.81	0.38	0.13	0.453	1.49	0.664	0.462	1.48
Si	100	53	20	32.3	172	104	34.9	169
Sm	0.00261	0.00176	0.00067	0.000800	0.00620	0.00260	0.000845	0.00568
Sn	0.163	0.150	0.057	0.0500	0.430	0.0900	0.0515	0.414
Sr	2.38	1.54	0.58	0.870	4.56	1.98	0.882	4.53
Tb	0.00040	0.00031	0.00012	0.000070	0.00100	0.000400	0.000075	0.000910
Th	0.0044	0.0027	0.0010	0.000900	0.00900	0.00450	0.00105	0.00849
Ti[a]	1.06	0.45	0.19	0.700	1.82	0.910	0.700	1.76
Tl	0.00157	0.00097	0.00037	0.000300	0.00300	0.00130	0.000420	0.00297
Tm	0.000239	0.000120	0.000045	0.000130	0.000470	0.000200	0.000132	0.000448
U	0.0052	0.0092	0.0035	0.000810	0.0261	0.00187	0.000902	0.0227
Y	0.0112	0.0075	0.0028	0.000500	0.0250	0.0100	0.00157	0.0235
Yb	0.00144	0.00104	0.00039	0.000500	0.00340	0.00110	0.000515	0.00324
Zn	903	454	144	277	1707	818	328	1663
Zr	0.036	0.029	0.011	0.0100	0.0900	0.0200	0.0100	0.0840

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

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

Table 5 Basic statistical parameters of trace element mass fraction (mg/kg, dry mass basis) in the nonhyperplastic prostate gland of males of ages 41–87 years (the age group 2 and 3 combined, n=37)

Element	M	SD	SEM	Min	Max	Median	P0.025	P0.975
Ag	0.0380	0.0296	0.0056	0.00500	0.155	0.0300	0.00838	0.0976
Al	34.1	17.7	3.5	9.60	73.3	29.0	12.0	70.8
Au	0.00412	0.00346	0.00078	0.00100	0.0106	0.00230	0.00100	0.0103
B	1.04	0.85	0.18	0.300	3.00	0.700	0.300	2.89
Ba	1.48	1.01	0.21	0.200	4.33	1.17	0.299	3.73
Be	0.000942	0.000354	0.000072	0.000700	0.00210	0.000750	0.000700	0.00187
Bi	0.029	0.056	0.011	0.00100	0.205	0.00560	0.00130	0.200
Br	34.6	17.3	3.2	12.0	80.7	30.9	12.4	68.3
Ca	2428	1232	233	1180	6893	2195	1197	5553
Cd	1.12	0.64	0.13	0.320	2.40	0.985	0.320	2.39
Ce	0.0309	0.0244	0.0050	0.00600	0.0960	0.0220	0.00600	0.0937
Cl	13,622	2111	668	10,100	16,200	14,450	10,363	16,178
Co	0.0467	0.0354	0.0064	0.0165	0.200	0.0400	0.0169	0.130
Cr	0.562	0.433	0.082	0.0300	1.81	0.456	0.0300	1.67
Cs	0.0339	0.0170	0.0033	0.0100	0.0870	0.0300	0.0131	0.0720
Cu	9.85	4.66	0.97	4.10	22.2	8.30	4.98	19.8
Dy	0.00293	0.00242	0.00049	0.000690	0.0104	0.00224	0.000696	0.00934
Er	0.00148	0.00114	0.00023	0.000400	0.00530	0.00116	0.000446	0.00421
Fe	121	34.0	5.9	62.0	210	114	67.6	192
Gd	0.00290	0.00199	0.00041	0.000600	0.00850	0.00235	0.000715	0.00735
Hg	0.0521	0.0426	0.0075	0.00770	0.147	0.0335	0.0165	0.141
Ho	0.000567	0.000397	0.000079	0.000160	0.00179	0.000450	0.000172	0.00139
K	11,650	2340	434	6325	18,198	11,403	7352	15,489
La	0.080	0.100	0.020	0.00900	0.324	0.0335	0.00963	0.309
Li	0.0419	0.0264	0.0055	0.0150	0.101	0.0300	0.0161	0.100
Mg	1071	409	76	447	2060	1017	520	1955
Mn	1.32	0.42	0.09	0.750	2.80	1.30	0.836	2.23
Mo	0.282	0.190	0.038	0.100	0.850	0.230	0.100	0.754
Na	10,987	2158	394	6415	15,300	10,911	6719	15,151
Nb	0.0054	0.0058	0.0012	0.00100	0.0200	0.00310	0.00100	0.0194
Nd	0.0137	0.0100	0.0021	0.00300	0.0420	0.0100	0.00300	0.0354
Ni	3.10	2.49	0.51	0.200	9.50	2.85	0.373	8.29
P	7617	1839	368	5969	14,838	7225	6017	11,741
Pb	2.39	2.85	0.56	0.150	10.7	0.830	0.181	9.39
Pr	0.00353	0.00258	0.00053	0.000600	0.0106	0.00285	0.000715	0.00939
Rb	14.5	5.06	0.9	5.90	26.5	14.2	6.23	25.5
S	8657	1271	254	5662	12,567	8569	6680	11,366
Sb	0.0427	0.0364	0.0063	0.00800	0.158	0.0375	0.00960	0.154
Sc	0.0294	0.0236	0.0053	0.00460	0.0771	0.0200	0.00660	0.0768
Se	0.748	0.266	0.047	0.318	1.49	0.735	0.348	1.44
Si	102	55	11	32.3	235	94.1	37.0	205
Sm	0.00267	0.00176	0.00035	0.000600	0.00700	0.00260	0.000660	0.00652
Sn	0.320	0.322	0.063	0.0500	1.11	0.140	0.0563	1.04
Sr	2.47	1.98	0.41	0.870	8.90	1.60	0.914	6.87
Tb	0.000393	0.000301	0.000062	0.000070	0.00120	0.000350	0.000070	0.00109
Th	0.00335	0.00363	0.00074	0.000500	0.0172	0.00180	0.000558	0.0125
Ti[a]	2.82	3.07	0.64	0.700	13.7	1.82	0.700	10.1
Tl	0.00138	0.00072	0.00015	0.000300	0.00300	0.00130	0.000415	0.00289
Tm	0.000241	0.000169	0.000035	0.000040	0.000830	0.000200	0.000063	0.000623
U	0.0070	0.0105	0.0021	0.000790	0.0381	0.00261	0.000802	0.0341
Y	0.0187	0.0217	0.0043	0.000500	0.0840	0.0100	0.00206	0.0765
Yb	0.00141	0.00121	0.00025	0.000200	0.00510	0.00110	0.000315	0.00412
Zn	1072	749	123	229	4298	915	244	2249
Zr	0.0358	0.0272	0.0055	0.0100	0.0900	0.0250	0.0100	0.0900

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

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

Table 6 Ratio of mean values (M) and the reliability of difference between mean values of trace element mass fractions in prostate glands of our different age groups

Element	Ratio of means				The reliability of difference between means (Student's *t* test, $p\leq$)			
	M_2/M_1	M_3/M_1	M_3/M_2	M_{2+3}/M_1	G_1-G_2	G_1-G_3	G_2-G_3	$G_1-(G_2+G_3)$
Ag	0.75	0.50	0.67	0.67	0.213	*0.011*	0.160	0.069
Al	1.06	1.08	1.02	1.07	0.768	0.728	0.917	0.716
Au	0.75	1.52	2.03	0.98	0.404	0.315	0.128	0.927
B	1.34	1.39	1.04	1.35	0.287	0.394	0.911	0.173
Ba	0.96	2.04	2.14	1.29	0.823	*0.049*	*0.042*	0.222
Be	1.03	1.03	1.00	1.03	0.754	0.885	0.993	0.758
Bi	8.68	1.83	0.21	6.62	*0.043*	0.267	0.071	*0.036*
Br	1.02	1.07	1.06	1.08	0.721	0.745	0.983	0.708
Ca	1.24	0.93	0.75	1.15	0.167	0.610	0.099	0.278
Cd	1.83	2.00	1.09	1.88	*0.004*	0.092	0.765	*0.001*
Ce	1.57	1.34	0.85	1.50	0.142	0.445	0.642	0.127
Cl	1.15	1.10	0.96	1.13	0.232	0.563	0.745	0.259
Co	1.40	1.83	1.31	1.53	*0.039*	0.206	0.497	*0.024*
Cr	1.06	1.56	1.47	1.19	0.803	0.245	0.300	0.435
Cs	1.01	0.89	0.89	0.97	0.971	0.575	0.592	0.830
Cu	0.96	0.70	0.73	0.90	0.836	0.101	0.122	0.497
Dy	1.12	1.38	1.24	1.19	0.701	0.517	0.658	0.530
Er	1.02	1.08	1.06	1.04	0.944	0.809	0.849	0.890
Fe	1.25	1.17	0.94	1.22	*0.012*	0.182	0.564	*0.009*
Gd	1.27	1.30	1.02	1.28	0.415	0.442	0.939	0.352
Hg	1.67	1.06	0.64	1.49	*0.029*	0.884	0.172	*0.050*
Ho	1.23	1.15	0.93	1.21	0.496	0.660	0.819	0.496
K	0.92	0.88	0.96	0.91	0.162	0.143	0.669	0.093
La	1.59	0.54	0.34	1.31	0.261	0.270	*0.037*	0.487
Li	1.04	1.11	1.07	1.06	0.868	0.774	0.846	0.786
Mg	0.94	0.85	0.90	0.92	0.642	0.273	0.469	0.469
Mn	0.87	0.81	0.93	0.85	0.192	*0.043*	0.545	0.092
Mo	1.10	0.66	0.60	0.98	0.616	*0.020*	*0.027*	0.918
Na	1.02	1.09	1.07	1.04	0.750	0.346	0.444	0.519
Nb	1.68	1.02	0.61	1.48	0.194	0.961	0.216	0.245
Nd	1.36	1.27	0.94	1.34	0.288	0.490	0.828	0.255
Ni	0.83	0.67	0.81	0.78	0.422	0.107	0.500	0.231
P	1.00	0.92	0.91	0.98	0.952	0.261	0.293	0.770
Pb	2.39	1.87	0.78	2.25	0.073	0.335	0.622	*0.050*
Pr	1.43	1.28	0.90	1.38	0.214	0.513	0.735	0.207
Rb	0.98	0.83	0.85	0.94	0.846	0.121	0.193	0.451
S	0.96	1.02	1.06	0.97	0.321	0.734	0.302	0.473
Sb	0.98	0.86	0.88	0.94	0.924	0.558	0.660	0.723
Sc	2.20	1.44	0.65	2.09	*0.019*	0.437	0.259	*0.015*
Se	1.06	1.19	1.12	1.10	0.499	0.349	0.518	0.295
Si	0.95	0.93	0.98	0.95	0.809	0.780	0.930	0.770
Sm	1.33	1.29	0.97	1.32	0.310	0.490	0.921	0.291
Sn	3.04	1.31	0.43	2.58	*0.007*	0.545	*0.039*	*0.007*
Sr	1.78	1.69	0.95	1.75	0.098	0.174	0.881	0.051
Tb	1.34	1.37	1.02	1.34	0.360	0.472	0.981	0.313
Th	1.79	2.70	1.51	2.06	0.209	*0.034*	0.311	*0.037*

Table 6 (continued)

Element	Ratio of means				The reliability of difference between means (Student's *t* test, $p\leq$)			
	M_2/M_1	M_3/M_1	M_3/M_2	M_{2+3}/M_1	G_1-G_2	G_1-G_3	G_2-G_3	$G_1-(G_2+G_3)$
Ti[a]	1.90	0.58	0.31	1.55	0.106	0.187	*0.011*	0.236
Tl	0.93	1.11	1.20	0.98	0.611	0.682	0.521	0.908
Tm	1.07	1.05	0.99	1.06	0.843	0.877	0.961	0.839
U	3.67	2.48	0.68	3.33	*0.050*	0.407	0.586	*0.032*
Y	1.32	0.69	0.52	1.15	0.453	0.314	0.117	0.673
Yb	1.07	1.10	1.03	1.08	0.847	0.802	0.934	0.812
Zn	1.99	1.58	0.80	1.88	*0.002*	*0.049*	0.288	*0.0004*
Zr	0.78	0.78	1.00	0.78	0.577	0.615	0.990	0.567

Statistically significant values of *p* are in italics

$M_{1,2,3}$ arithmetic mean in age group (G) 1, 2, and 3, respectively, M_{2+3} arithmetic mean in age group 2 and 3 combined (see Table 5).

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

obtained with nondestructive (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 (Tables 2, 3, 4, and 5). The fact that the elemental mass fractions (M±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 [20–23, 25] suggests an acceptable accuracy of the measurements performed on our prostate tissue samples.

The mass fractions for 54 chemical elements listed in Tables 2, 3, 4, and 5 (Ag, Al, Au, B, Ba, Be, Bi, Br, Ca, Cd, Ce, Cl, Co, Cr, Cs, Cu, Dy, Er, Fe, Gd, Hg, Ho, K, La, Li, Mg, Mn, Mo, Na, Nb, Nd, Ni, P, Pb, Pr, Rb, S, Sb, Sc, Se, Si, Sm, Sn, Sr, Tb, Th, Ti, Tl, Tm, U, Y, Yb, Zn, and Zr) were measured in the total, or in a major portion, of the prostate samples investigated. This allowed calculation of the mean values and selected statistical features for these elements for all age groups.

In the histologically normal prostates, we have observed an increase (more than 10 %) in mass fraction of B, Bi, Ca, Cd, Ce, Cl, Co, Dy, Fe, Gd, Hg, Ho, La, Nb, Nd, Pb, Pr, Sc, Sm, Sn, Sr, Tb, Th, Ti, U, Y, and Zn with age from 21 to 60 years. In particular, a significant tendency of age-related increase in Bi ($p\leq0.043$), Cd ($p\leq0.004$), Co ($p\leq0.039$), Fe ($p\leq0.012$), Hg ($p\leq0.029$), Sc ($p\leq0.019$), Sn ($p\leq0.007$), U ($p\leq0.050$), and Zn ($p\leq0.003$) mass fractions was observed in prostate (Table 6). For example, in prostates of group 2, the Bi mass fractions were almost nine times, and the Cd, Hg, Sc, Sn, U, and Zn mass fractions were approximately 2–4 times, greater than in prostate of members of group 1 (Table 6).

From the comparison of the mass fraction means in the three age groups (Table 6), it followed that the mass fraction of Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, Th, U, and Zn increased in the age range 21–60 years and reached a maximum somewhere in the sixth decade (Fig. 1). In the histologically normal prostates of men in the age range 61–87 years, the mass fractions of all these elements were maintained at approximately constant levels (after comparison between the age groups 2 and 3, Table 6). Thus, the main changes of chemical element contents with age in prostate tissue are found between the ages 21 and 60 years, but element mass fractions in the geriatric prostate hardly differ from those in prostate glands of adult males aged 41 to 60 years with the exception of Ba, La, Mo, Sn, and Ti. The Ba mass fraction increased, with statistical significance (Table 6, Fig. 1), for ages after 61 years. The La, Mo, Sn, and Ti mass fractions decreased with age after 60 years, in the comparison with those in the age range 41–60 years, but remained above values seen in the age range 21–40 years, with the exception of Mn and Mo (Table 6).

The prevalence of prostate diseases, particularly PCa, increases drastically after age 40 years [1, 2, 5–7]. Thus, because there is much interest in studying differences in chemical element contents before and after 40, the group 2 (41 to 60) and 3 (61 to 87) years were combined. From the comparison between the mass fraction means of group 1 with those in groups 2 and 3 combined (Table 6), it followed that the mass fractions of Bi ($p\leq0.036$), Cd ($p\leq0.001$), Co ($p\leq0.024$), Fe ($p\leq0.009$), Hg ($p\leq0.050$), Pb ($p\leq0.050$), Sc ($p\leq0.015$), Sn ($p\leq0.007$), Th ($p\leq0.037$), U ($p\leq0.032$), and Zn ($p\leq0.0004$) were statistically significant higher in the age range 41–87 years. It was not found, for any chemical element from the 67 investigated in this study, that the level of any elemental mass fraction was statistically significantly lower after the age of 40 years.

A change of Ba, Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, and Zn mass fractions in the prostate tissue with age from 21 to 87 years is more ideally fitted by a polynomial law (Fig. 1). An increase of Th and U mass fraction is more ideally fitted by a logarithmic law (Fig. 1).

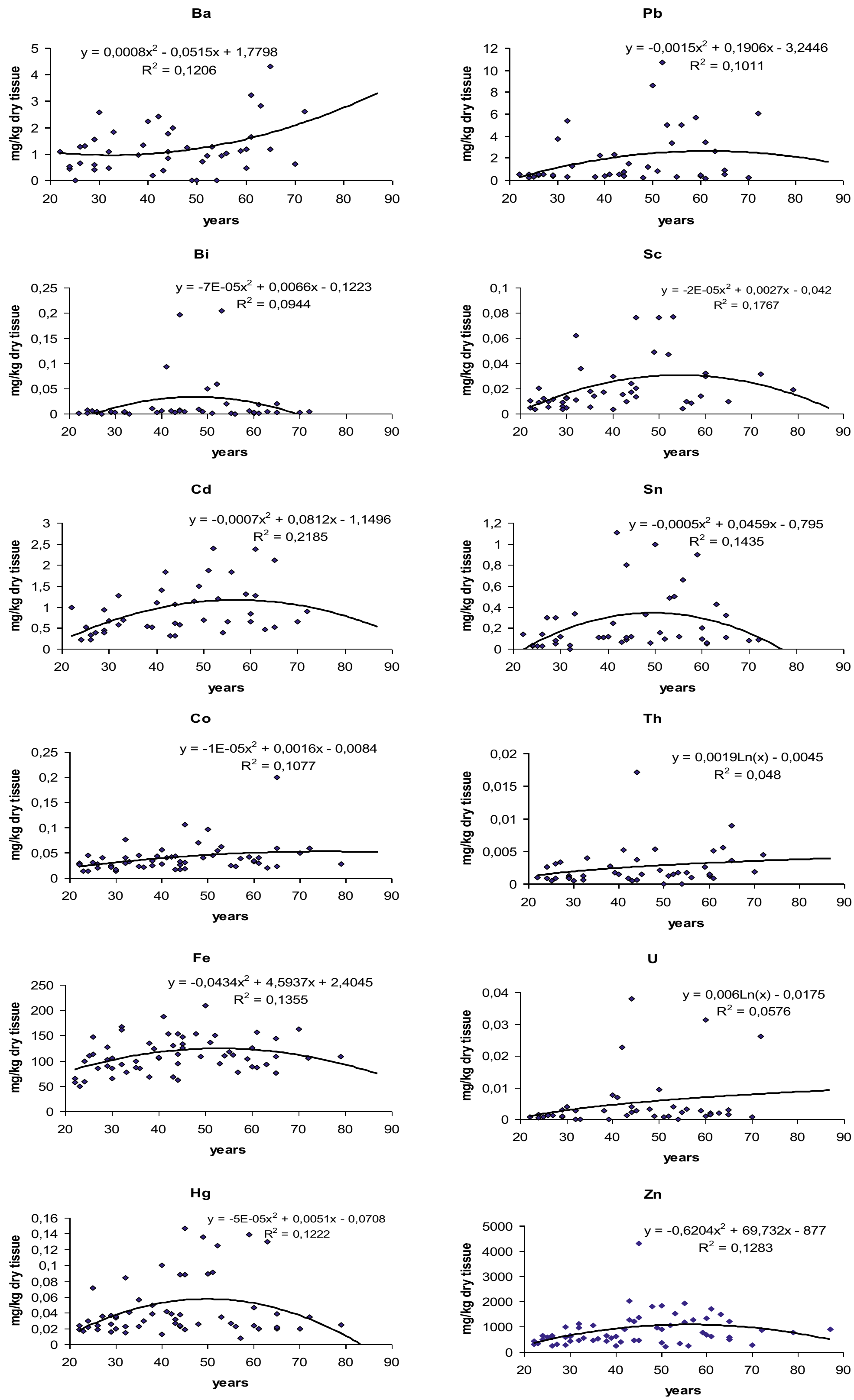

Fig. 1 Individual data sets for the Ba, Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, Th, U, and Zn mass fractions in the nonhyperplastic prostate gland of males aged between 21 and 87 years and their trend lines

The variations of the individual mass fractions of many chemical elements increased with age. This conclusion followed from the qualitative analysis of individual data sets (Fig. 1) and the quantitative comparison of the values of relative standard deviations (M/SD, %) in the age group 1 and 2 (Tables 2 and 3), for example, for Bi (54 % *v* 168 %), Hg

Table 7 Median, minimum, and maximum value of means of trace element mass fractions (mg/kg, on dry mass basis) in prostate tissue of adult males according to data from the literature in comparison with this works' results for males aged 21-87 years

Element	Published data [Reference]			This work
	Median of means, (*n*)*	Minimum of means M or M±SD, (*n*)**	Maximum of means M or M±SD, (*n*)**	M±SD *n*=65
Ag	0.055 (11)	<0.006 (48) [33]	0.24 (7) [34]	0.047±0.036
Al	34.0 (9)	13±66 (50) [33]	80±98 (9) [35]	33±18
As	0.018 (5)	0.0051 (21) [36]	0.045±0.022 (10) [37]	≤0.018
Au	0.0053 (7)	0.0032±0.0027 (21) [38]	1.5 (3 [34]	0.0042±0.0037
B	1.0 (10)	<0.47 (50) [33]	5.9±17.2 (21) [38]	0.94±0.70
Ba	1.75 (10)	0.12 (50) [33]	102±82 (10) [39]	1.34±0.89
Be	0.00095 (5)	0.00091±0.00026 (28) [40]	0.003±0.005 (16) [28]	0.00093±0.00032
Bi	0.018 (6)	0.0039±0.0017 (16) [29]	<0.09 (50) [33]	0.020±0.046
Br	30 (18)	14±9 (4) [41]	50±32 (10) [42]	34±23
Ca	1990 (22)	427±117 (21) [43]	7500±12,300 (57) [32]	2285±1066
Cd	0.78 (26)	0.07 (129) [44]	427±497 (55) [45]	0.91±0.59
Ce	0.028 (5)	0.019±0.020 (16) [29]	0.049±0.066 (16) [28]	0.027±0.022
Cl	12,450 (9)	4929±412 (27) [46]	14,770±1528 (64) [47]	12,791±3206
Co	0.036 (12)	0.022±0.010 (16) [26]	12 (9) [35]	0.039±0.028
Cr	0.51 (15)	0.053 (50) [33]	29.4±5.9 (5) [48]	0.52±0.42
Cs	0.036 (7)	0.031±0.016 (10) [40]	3.5 (12) [49]	0.034±0.015
Cu	9.6 (28)	1.37 (–) [50]	1488±47 (10) [51]	10.3±4.9
Dy	0.0030 (5)	0.0021±0.0018 (16) [29]	0.008±0.010 (16) [28]	0.0027±0.0023
Er	0.0015 (5)	0.0011±0.0011 (16) [29]	0.004±0.006 (16) [28]	0.0015±0.0013
Eu	≤0.0006 (3)	≤0.00049 (28) [40]	≤0.0012 (16) [28]	≤0.00054
Fe	118 (34)	5.7±0.1 (5) [52]	1224±76 (10) [51]	111±34
Ga	≤0.080 (3)	≤0.036 (10) [40]	≤0.093 (28) [40]	≤0.081
Gd	0.0029 (5)	0.0019±0.0017 (16) [29]	0.007±0.009 (16) [28]	0.0026±0.0021
Hf	≤0.02 (3)	≤0.015 (10) [40]	≤0.049 (16) [28]	≤0.018
Hg	0.037 (10)	0.024±0.014 (16) [26]	0.65±0.58 (5) [37]	0.044±0.036
Ho	0.00057 (5)	0.00038±0.00037 (16) [29]	0.001±0.002 (16) [28]	0.00053±0.00043
Ir	≤0.00044 (3)	≤0.00038 (28) [40]	≤0.00054 (16) [28]	≤0.00042
K	11,800 (20)	4360±70 (27) [46]	13,000±660 (21) [53]	12,206±2591
La	0.048 (5)	0.016±0.012 (16) [29]	0.097±0.111 (27) [40]	0.073±0.092
Li	0.041 (8)	0.040±0.024 (64) [22]	0.064±0.049 (16) [28]	0.041±0.026
Lu	≤0.00022 (3)	≤0.00020 (10) [40]	≤0.00063 (16) [28]	≤0.00022
Mg	1120 (21)	498±172 (13) [32]	2056±476 (21) [43]	1115±472
Mn	1.48 (24)	<0.47 (12) [49]	106±18 (5) [48]	1.42±0.45
Mo	0.29 (7)	<0.19 (50) [33]	1.8 (2) [34]	0.28±0.17
Na	10,500 (16)	23±26 (13) [32]	13,700±3500 (4) [54]	10,790±2380
Nb	0.0044 (5)	0.0023±0.0021 (16) [29]	0.013±0.020 (16) [28]	0.0047±0.0051
Nd	0.013 (5)	0.0095±0.0087 (16) [29]	0.025±0.034 (16) [28]	0.0122±0.0095
Ni	4.0 (10)	0.18 (4) [55]	14.1±4.2 (27) [46]	3.5±2.3
P	7120 (15)	2060±690 (13) [32]	14,500 (12) [49]	7679±1710
Pb	1.3 (17)	0.15 (41) [56]	9.4 (4) [54]	1.9±2.5
Pd	≤0.0073 (3)	≤0.0070 (64) [23]	≤0.014 (16) [28]	≤0.0074
Pr	0.0033 (5)	0.0024±0.0025 (16) [29]	0.006±0.008 (16) [28]	0.0031±0.0025
Pt	≤0.00062 (3)	≤0.00056 (28) [40]	≤0.0029 (16) [28]	≤0.00059
Rb	14.2 (16)	5.9 (9) [35]	68±39 (4) [54]	14.9±4.6
Re	≤0.0010 (3)	≤0.00099 (28) [40]	≤0.0048 (64) [28]	≤0.0010
Rh	<0.01 (1)	<0.01 (50) [29]	<0.01 (50) [29]	<0.01

Table 7 (continued)

Element	Published data [Reference]			This work
	Median of means, (*n*)*	Minimum of means M or M±SD, (*n*)**	Maximum of means M or M±SD, (*n*)**	M±SD *n*=65
S	7370 (6)	5300±750 (57) [32]	9820±1710 (21) [53]	8750±1098
Sb	0.046 (10)	0.039±0.026 (10) [40]	0.42±0.56 (7) [37]	0.043±0.034
Sc	0.014 (8)	0.0085±0.0102 (16) [51]	0.031±0.025 (27) [47]	0.021±0.020
Se	0.73 (22)	0.32 (129) [44]	18.8±2.4 (27) [46]	0.72±0.25
Si	100 (6)	51 (1) [57]	111±64 (64) [22]	104±60
Sm	0.0027 (5)	0.0017±0.0016 (16) [29]	0.006±0.008 (16) [28]	0.0024±0.0019
Sn	0.25 (9)	0.11±0.10 (16) [29]	4.4 (7) [34]	0.25±0.28
Sr	1.46 (13)	0.75±0.75 (48) [33]	2.6±3.1 (27) [20]	2.03±1.80
Ta	≤0.0050 (3)	≤0.0047 (10) [40]	≤0.010 (16) [28]	≤0.0053
Tb	0.00040 (5)	0.00021±0.00021 (16) [29]	0.001±0.002 (16) [28]	0.00035±0.00031
Te	<0.003 (4)	<0.003 (65) [40]	193 (2) [54]	<0.003
Th	0.0027 (5)	0.0015±0.0010 (16) [29]	0.008±0.011 (16) [28]	0.0026±0.0030
Ti	2.8 (10)	<0.29 (50) [33]	156±9 (27) [46]	2.4±2.7[a]
Tl	0.0014 (7)	0.00131±0.00061 (27) [40]	0.59 (1) [34]	0.00139±0.00064
Tm	0.00024 (5)	0.00018±0.00019 (16) [29]	0.0006±0.0009 (16) [28]	0.00024±0.00020
U	0.0049 (6)	0.0015±0.0011 (16) [29]	0.4 (1) [58]	0.0052±0.0088
V	≤0.21 (4)	<0.047 (50) [33]	41±12 (5) [48]	≤0.22
Y	0.020 (3)	0.0087±0.0080 (16) [29]	112 (12) [49]	0.036±0.054
Yb	0.0014 (4)	0.0013±0.0015 (28) [40]	0.0037±0.0062 (16) [28]	0.0037±0.0062
Zn	525 (75)	101 (1) [59]	3218±41 (10) [51]	856±634
Zr	0.045 (5)	0.036±0.027 (27) [40]	0.16±0.21 (16) [28]	0.040±0.046

M arithmetic mean, *SD* standard deviation, *(n)** no. of references contribution to this value, *(n)*** no. of samples

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

(62 % *v* 76 %), Sn (82 % *v* 93 %), Th (67 % *v* 135 %), U (92 % *v* 145 %), and Zn (41 % *v* 73 %). Of course, individual variation of consumption of pharmaceuticals, dietary, environmental, occupational, and some other factors influence the levels of chemical elements in the prostate at different times during the lifespan. In addition, in our previous studies, it was shown that many chemical elements bind tightly with one of the histological structures of prostate glands such as stroma, epithelial cells, and glandular lumen [24, 38, 53, 65–67]. It was also found that the percent volumes of these histological structures depend from age and the individual uroflowmetric characteristics of the subject [68]. Moreover, the variations of the individual percent volumes of histological structures and uroflowmetric characteristics also increase with age [24, 67, 68].

The mean values obtained for the 67 chemical element mass fractions in adult and geriatric nonhyperplastic prostate glands (from adults aged 20–87 years) as shown in Table 7 agree well with median of means reported in the literature for the normal prostate tissue of adult males, including samples obtained from persons who died from different diseases. However, it must be remarked that the ranges of reported means, arising from both analytical uncertainty and individual variability of elemental mass fractions in the human prostate, are surprisingly wide (Table 7). For example, the "maximum mean/minimum mean" ratio for such elements as Ag, As, Au, B, Ba, Ca, Cd, Co, Cr, Cs, Cu, Fe, Hg, Mn, Mo, Na, Ni, Pb, Rb, Sb, Se, Sn, U, V, Y, and Zn is nearly equal one to five orders of magnitude.

This work's results for age dependence of Ca, Cd, Cu, K, Na, P, and Zn mass fractions in nonhyperplastic prostate glands (for adult and geriatric persons aged 20–87 years) are in accordance with earlier findings [30–32, 44, 56, 69, 70]. For example, Hienzsch et al. [30] found that the Zn mass fraction in the normal prostate was higher in the age group 51–70 years than in the age group 31–50 years by approximately 1.8 times and somewhat lower (but the difference was not statistically significant) in the age group 71–90 years, compared with the age group 51–70 years. An increase of Cd mass fraction in the prostate tissue with age was found by Hienzsch et al. [69], Oldereid et al. [56], and Schöpfer et al. [44]. In accordance with Tohno et al. [32], there were no significant correlations between age and the Fe, Mg, Na, and Zn mass fractions in prostate tissue of Thai subjects, whose ages ranged from 43 to 86 years, and of Japanese subjects, with age from 65 to 101 years. These conclusions agree with our results.

In our earlier publications, it was discussed in detail [13, 15, 67] that the age-related excessive Zn level in prostatic tissue is probably one of the main factors influencing the enlargement of the prostate gland, as well as the initiation and progression of PCa. In addition to the elevated Zn level, an age-related increase and excess in Ba, Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, Th, and U mass fractions in prostatic tissue may contribute to harmful effects on the gland. There are good reasons for such speculations since many reviews and numerous papers raise the concern about toxicity and carcinogenicity of these metals [71–85]. Each of these metals is distinct in its primary mode of action. Moreover, there are several forms of synergistic action of these metals as a part of intracellular metabolism, during which several reactive intermediates and byproducts are created [71, 72, 82]. These reactive species are capable of potent and surprisingly selective activation of stress-signaling pathways, inhibition of DNA metabolism, repair, and formation of DNA crosslinks, which are known to contribute to the development of human cancers [72, 74, 78]. In addition to genetic damage via both oxidative and nonoxidative (DNA adducts) mechanisms, metals can also cause significant changes in DNA methylation and histone modifications, leading to alterations in gene expression [74, 75, 77, 81]. In vitro and animal carcinogenic studies provided strong support for the idea that metals can also act as co-carcinogens in combination with nonmetal carcinogens [74, 83].

Multiple studies put forward an idea that due to lifestyle, dietary habits, and physiological effects of aging, the elderly male population is predisposed to Ca, Cu, Fe, Mg, Se, Zn, and some other chemical element deficiencies [86–90], which can increase this population's susceptibility to BPH and PCa [91]. Our data reveal that there are no age-related deficiencies in Ca, Cu, Fe, Mg, Se, Zn, and other chemical elements investigated in the prostate tissue. Moreover, the mean mass fractions of Ca, Fe, Se, and Zn for the group of adult males aged 41 years and older are higher than for those younger than 40 years. Thus, "the potential role of age-related deficiency of Ca, Cu, Fe, Mg, Se, Zn" [91] or other chemical elements in the prostate has not been confirmed by us as being involved in the etiology of BPH and PCa.

Conclusion

The combination of nuclear and inductively coupled plasma analytical methods allows an estimation of the contents of no less than 67 chemical elements and a precise determination of the mass fraction of 54 elements in the tissue samples of nonhyperplastic adult and geriatric prostate glands.

This work's results reveal that there is a significant tendency for an increase in Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, Th, U, and Zn mass fractions in the prostate tissue of healthy individuals, as their ages vary from 21 up to 60 years, as well as an increase in prostatic Ba from age 61 up to 87 years. These findings imply that an age-related increase and excess in Ba, Bi, Cd, Co, Fe, Hg, Pb, Sc, Sn, Th, U, and Zn mass fraction in prostatic tissue may be one of the main factors in the etiology of BPH and PCa.

The mean values obtained for the 67 chemical element mass fractions in adult and geriatric nonhyperplastic prostate glands agree well with median of means reported in the literature. However, the ranges of reported means are extremely wide.

All the prostates studied had normal morphology and were obtained from subjects without systematic or chronic disorders. Thus, our data for 54 chemical element mass fractions in nonhyperplastic adult and geriatric prostate glands at least may serve as indicative normal values for an urban population of the Russian Central European region.

The data obtained in the present study may also prove very valuable for many different applications in environmental and occupational medicine, medical radiology, radiation protection, radiotherapy dosimetry, and other scientific fields.

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