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Research Article

Ratio of Zinc to Bromine, Iron, Rubidium, and Strontium Concentration in the Prostatic Fluid of Patients with Benign Prostatic Hyperplasia

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Abstract

Introduction: Benign prostatic hyperplasia (BPH) is a benign tumor that infects almost all men as they get older. To date, we still have no precise knowledge of the biochemical, cellular and molecular processes underlying the pathogenesis of BPH. One of the main functions of prostate gland is a production of prostatic fluid with extremely high concentration of Zn and elevated level some other TE and electrolytes. The aim of this exploratory study was to evaluate changes in the levels of Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr concentration ratio in prostatic fluid of the hyperplastic prostate.

Methods: Prostatic fluid levels of Br, Fe, Rb, Sr, and Zn were prospectively evaluated in 52 patients with BPH and 38 healthy male inhabitants. Measurements were performed using 109Cd radionuclide-induced energy dispersive X-ray fluorescent microanalysis. Using obtained results the individual values of Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr concentration ratio were calculated.

Results: Mean values ± standard error of means for Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr concentration ratio in the prostatic fluid of normal prostate were: 639 ± 122, 120 ± 19, 637 ± 69, and 733 ± 116, respectively. It was observed that in the secret of hyperplastic prostate ratios of Zn/Br, Zn/Fe, and Zn/Rb some decreased in a comparison with those in the secret of normal prostate however the found differences were not statistically significant.

Conclusions: The alterations in levels of Zn and Rb in the EPF of hyperplastic prostate might demonstrate an involvement of these trace elements in etiology and pathogenesis of BPH. In spite of opposite directions in changes of Zn and Rb contents in EPF of BPH prostate the alteration in level of Zn/Rb ratio was not statistically significant. In our opinion, found changes in TE contents and their ratios in EPF of BPH prostate could indicate a suppression of specific functional activity of the gland.

Keywords: Benign Prostatic Hyperplasia; Prostatic Fluid; Trace Elements; Trace Element Ratios; Energy-Dispersive X-Ray Fluorescent Analysis

Abbreviations

BPH: Benign Prostatic Hyperplasia; TE: Trace Elements; Br: Bromine; Fe: Iron; Rb: Rubidium; Sr: Strontium; Zn: Zinc; EPF: Expressed Prostatic Fluid; EDXRF: Energy Dispersive X-Ray Fluorescence Analysis; CRM: Certified Reference Materials; IAEA: International Atomic Energy Agency.

Introduction

Benign prostatic hyperplasia (BPH) is a benign tumor that develops in men and represents the most common urologic disease among them after the age of fifty [1-3]. BPH is histologically defined as an overgrowth of the epithelial and stromal cells from the transition zone and periurethral area of prostate [4,5]. The excessive cell proliferation associated with BPH causes benign prostatic enlargement, bladder outlet obstruction, and lower urinary tract symptoms, which afflict the patients [3]. Prostate enlargement infects almost all men as they get older. Incidence of histological BPH could be over 70% at 60 years old and over 90% at 70 years old [1,6]. To date, we still have no precise knowledge of the biochemical, cellular and molecular processes underlying the pathogenesis of BPH. Although the influence of androgens and estrogens has been demonstrated, hormonal factors alone may not fully explain BPH development [7,8].

Although the etiology of BPH is unknown, several risk factors including micronutrients such as trace elements (TE) zinc (Zn), iron (Fe), selenium (Se) and some others have been identified [9-11]. TEs have essential physiological functions. They include maintenance and regulation of cell function, gene regulation, activation or inhibition of enzymatic reactions, and regulation of membrane function. Essential or toxic (mutagenic, carcinogenic) properties of TE depend on tissue-specific need or tolerance, respectively [12]. Insufficient or excessive accumulation, as well as an imbalance of the TE may disturb the cell functions and may result in cellular degeneration, death or, on the contrary, intensive proliferation [13]. In our previous studies a significant involvement of Zn, calcium (Ca), magnesium (Mg), rubidium (Rb) and some other TE in the function of prostate was observed [14-24].

One of the main functions of prostate gland is a production of prostatic fluid [25] with extremely high concentration of Zn and elevated level of Ca, Mg, Rb, and some other TE and electrolytes in a comparison with those in serum and other fluids of human body. Samples of human expressed prostatic fluid (EPF) can be obtained using standard rectal massage procedure. Other words, EPF can be used in clinical studies as a liquid biopsy of prostate gland. The findings of the excess or deficiency in TE and the perturbation in their relationships in EPF of hyperplastic prostate may highlight the role of these disturbances in etiology of BPH and may be useful in diagnosis of disease. Unfortunately, data on the prostatic fluid TE of normal and hyperplastic prostate are very short. The first finding of remarkable high level of Zn concentration in human EPF was reported in the beginning of 1960s [26]. Analyzing EPF expressed from prostate of 8 apparently healthy men aged 25-55 years it was found that Zn concentration varied in range from 300 to 730 mg/L. After this finding several investigators have suggested that the measurement of Zn level in EPF may be useful as a marker of prostate secretory function [27,28]. It promoted a more detailed study of Zn concentration in EPF of healthy subjects and in those with different prostate diseases, including BPH [28,29]. A detailed review of these studies, reflecting the contradictions within accumulated data, was given in our earlier publication [29]. Moreover, the method and apparatus for micro analysis of Br, Fe, Rb, Sr, and Zn in the EPF samples using energy dispersive X-ray fluorescence (EDXRF) activated by radiation of radionuclide source ^{109}Cd was developed by us [30].

Thus, data on changes of TE contents in EPF of patients with BPH are very important, because it can clarify our knowledge of BPH pathogenesis and may be useful as BPH diagnostic markers. In present study it was supposed by us that apart from total amounts of TE the ratios of Zn to some other TE content in EPF have to reflect a disturbance of prostate function. As far as our knowledge there are no any published data on TE ratios in prostatic fluids.

This work had three aims. The first aim was to assess the Br, Fe, Rb, Sr, and Zn concentration in the EPF samples obtained from apparently health persons and patients with BPH using ^{109}Cd EDXRF micro-method. The second aim was to evaluate the quality of obtained results and to compare these results with published data. The last aim was to calculate Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios and compare the values of these TE ratios in EPF samples of normal and hyperplastic prostate. All studies were approved by the Ethical Committees of the Medical Radiological Research Centre, Obninsk. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Material and Methods

Samples

Specimens of EPF were obtained from 38 men with apparently normal prostates (mean age ± Standard Deviation - 59 ± 11 years, range 41-82 years) and from 52 patients with BPH (mean age 63 ± 6 years, range 52-75 years) by qualified urologists in the Urological Department of the Medical Radiological Research Centre using standard rectal massage procedure. In all cases the diagnosis has been confirmed by clinical examination and additionally in cases of BPH by morphological results obtained during studies of biopsy and resected materials. Subjects were asked to abstain from sexual intercourse for 3 days preceding the procedure. Specimens of EPF were obtained in sterile containers which were appropriately labeled.

Sample preparation

Twice twenty µL (microliters) of fluid were taken by micropipette from every specimen for TE analysis, while the rest of the fluid was used for cytological and bacteriological investigations. The chosen 20µL of the EPF for TE analysis was dropped on 11.3 mm diameter disk made of thin, ash-free filter papers fixed on the Scotch tape pieces and dried in an exsiccator at room temperature. Then the dried sample was covered with 4 µm Dacron film and centrally pulled onto a Plexiglas cylindrical frame [30].

Certified reference materials

To determine concentration of the TE by comparison with a known standard, aliquots of solutions of commercial, chemically pure compounds were used for a device calibration [31]. The standard samples for calibration were prepared in the same way as the samples of prostate fluid. Because there were no available liquid Certified Reference Material (CRM) ten sub-samples of the powdery CRM IAEA H-4 (animal muscle) were analyzed to estimate the precision and accuracy of results. Every CRM subsample weighing about 3 mg was applied to the piece of Scotch tape serving as an adhesive fixing backing. An acrylic stencil made in the form of a thin-walled cylinder with 11.3 mm inner diameter was used to apply the sub-sample to the Scotch tape. The polished-end acrylic pestle which is a constituent of the stencil set was used for uniform distribution of the sub-sample within the Scorch surface restricted by stencil inner diameter. When the sub-sample was slightly pressed to the Scotch adhesive sample, the stencil was removed. Then the sub-sample was covered with 4 µm Dacron film. Before the sample was applied, pieces of Scotch tape and Dacron film were weighed using analytical balance. Those were again weighed together with the sample inside to determine the sub-sample mass precisely.

Instrumentation and methods

The facility for radionuclide-induced energy dispersive X-ray fluorescence included an annular ^{109}Cd source with an activity of 2.56 GBq, Si(Li) detector with electric cooler and portable multichannel analyzer combined with a PC. Its resolution was 270 eV at the 6.4 keV line. The facility functioned as follows. Photons with a 22.1 keV ^{109}Cd energy are sent to the surface of a specimen analyzed inducing the fluorescence K_α X-rays of trace elements. The fluorescence irradiation got to the detector through a 10 mm diameter collimator to be recorded. The duration of the Zn concentration measurement together with Br, Fe, Rb, and Sr was 60 min. The intensity of K_α-line of Br, Fe, Rb, Sr, and Zn for EPF samples and standards was estimated on calculation basis of the total area of the corresponding photopeak in the spectra.

Computer programs and statistic

All EPF samples for EDXRF were prepared in duplicate and mean values of TE contents were used in final calculation. Using the Microsoft Office Excel programs, the summary of statistics, arithmetic mean, standard deviation, standard error of mean, minimum and maximum values, median, percentiles with 0.025 and 0.975 levels was calculated for TE concentrations and Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr in EPF of normal and BPH prostate. The difference in the results between two groups of samples (normal prostate and BPH) was evaluated by the parametric Student's t-test and non-parametric Wilcoxon-Mann-Whitney U-test.

Results

Table 1 depicts our data for Br, Fe, Rb, Sr, and Zn mass fractions in ten sub-samples of certified reference material (CRM) IAEA H-4 (animal muscle) and the certified values of this material. Of 4 TE (Br, Fe, Rb, and Zn) with certified values for the CRM IAEA H-4 (animal muscle) we determined contents of all certified elements (Table 1). Mean values (M±SD) for Br, Fe, Rb, and Zn were in the range of 95% confidence interval. Good agreement of the TE contents analyzed by ^{109}Cd radionuclide-induced EDXRF with the certified data of CRM IAEA H-4 (Table 1) indicate an acceptable accuracy of the results obtained in the study of the prostatic fluid presented in Tables 2-4.

Element	Certified values			This work results
	Mean	95% confidence interval	Type	Mean ± SD
Fe	49	47 - 51	C	48 ± 9
Zn	86	83 - 90	C	90 ± 5
Br	4.1	3.5 – 4.7	C	5.0 ± 1.2
Rb	18	17 - 20	C	22 ± 4
Sr	0.1	-	N	<1

Table 1: EDXRF data of Br, Fe, Rb, Sr, and Zn contents in the IAEA H-4 (animal muscle) reference material compared to certified values (mg/kg, dry mass basis).

Mean: Arithmetical Mean; SD: Standard Deviation;

C: Certified Values; N: Non-Certified Values

Table 2 presents certain statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, percentiles with 0.025 and 0.975 levels) of the Br, Fe, Rb, Sr, and Zn concentrations as well as of the Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios in EPF of normal and BPH prostate.

Condition of prostate	Element	Mean	SD	SEM	Min	Max	Median	Per. 0.025	Per. 0.975
Norm	Br	2.86	2.93	0.59	0.490	8.53	1.20	0.496	8.53
41-82 years	Fe	8.30	7.62	1.42	1.27	39.8	7.33	1.29	23.5
n=38	Rb	1.16	0.52	0.10	0.376	2.45	1.03	0.422	2.38
	Sr	1.27	0.84	0.17	0.400	3.44	1.18	0.400	3.22
	Zn	598	207	34	253	948	560	278	942
	Zn/Br	639	610	122	43.0	1882	439	48.0	1882
	Zn/Fe	120	97	19	13.0	343	77.0	17.0	343
	Zn/Rb	637	372	69	119	1612	536	193	1516
	Zn/Sr	733	570	116	155	2321	602	166	2050
BPH	Br	2.32	1.84	0.30	0.230	8.70	1.62	0.268	5.84
52-75 years	Fe	11.5	10.8	1.8	1.06	54.1	9.31	1.09	38.9
n=52	Rb	1.70	1.41	0.23	0.210	5.04	1.46	0.254	5.04
	Sr	1.41	1.09	0.26	0.230	4.79	1.12	0.300	4.02
	Zn	488	302	42	45.0	977	427	81.4	962
	Zn/Br	437	545	88	10.5	2416	219	27.1	1874
	Zn/Fe	92	117	19	2.81	508	43.2	5.93	374
	Zn/Rb	471	459	74	49.0	1809	283	51.8	1793
	Zn/Sr	596	787	191	71.0	3361	277	74.8	2434

Table 2: Some basic statistical parameters of Br, Fe, Rb, Sr, and Zn concentration (mg/L) and also Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr concentration ratio in prostate fluid of health men and patients with BPH.

M: Arithmetic Mean; SD: Standard Deviation; SEM: Standard Error of Mean; Min: Minimum Value; Max: Maximum Value; Per. 0.025: Percentile with 0.025 Level; Per. 0.975: Percentile with 0.975 Level; DL: Detection Limit.

The comparison of our results with published data for Br, Fe, Rb, Sr, and Zn concentrations and also for Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios in EPF of normal and BPH prostate [26-28,32-35] is shown in Table 3.

Condition	Element or ratio	Published data [Reference]			This work results
		Median of means (n)*	Minimum of means M or M ± SD, (n)**	Maximum of means M ± SD, (n)**	M ± SD
Norm	Br	-	-	-	2.86 ± 2.93
	Fe	-	-	-	8.30 ± 7.62
	Rb	2.26 (1)	2.26 ± 1.28 (18) [28]	2.26 ± 1.28 (18) [28]	1.16 ± 0.52
	Sr	-	-	-	1.27 ± 0.84
	Zn	453 (19)	47.1(-) [32]	5185 ± 3737 (10) [33]	598 ± 207
	Zn/Br	-	-	-	639 ± 610
	Zn/Fe	-	-	-	120 ± 97
	Zn/Rb	-	-	-	637 ± 372
	Zn/Sr	-	-	-	733 ± 570
BPH	Br	-	-	-	2.32 ± 1.84
	Fe	-	-	-	11.5 ± 10.8
	Rb	2.35 (1)	2.35 ± 1.85 (11) [28]	2.35 ± 1.85 (11) [28]	1.70 ± 1.41
	Sr	-	-	-	1.41 ± 1.09
	Zn	459 (7)	268 (7) [34]	9870 ± 10130 (11) [33]	488 ± 302
	Zn/Br	-	-	-	437 ± 545
	Zn/Fe	-	-	-	92 ± 117
	Zn/Rb	-	-	-	471 ± 459
	Zn/Sr	-	-	-	596 ± 787

Table 3: Median, minimum and maximum value of means of Br, Fe, Rb, Sr, and Zn concentration (mg/L) and also Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr concentration ratio in prostate fluid of health men and patients with BPH according to data from the literature.

M: Arithmetic Mean; SD: Standard Deviation; (n)*: Number of All References; (n)**: Number of Samples.

The ratios of means and the differences between mean values of Br, Fe, Rb, Sr, and Zn concentrations and also Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios in EPF of normal and BPH prostate are presented in Table 4.

Ratio	Age groups				Ratios
	Norm	BPH	Student's t-test $p \leq$	*U*-test* *p*	BPH to Norm
Br	2.86 ± 0.59	2.32 ± 0.30	0.414	>0.05	0.81
Fe	8.30 ± 1.42	11.5 ± 1.8	0.171	>0.05	1.39
Rb	1.16 ± 0.10	1.70 ± 0.23	0.031	<0.01	1.47
Sr	1.27 ± 0.17	1.41 ± 0.26	0.660	>0.05	1.11
Zn	598 ± 34	488 ± 42	0.044	<0.01	0.82
Zn/Br	639 ± 122	437 ± 88	0.187	>0.05	0.68
Zn/Fe	120 ± 19	92 ± 19	0.309	>0.05	0.77
Zn/Rb	637 ± 69	471 ± 74	0.107	>0.05	0.74
Zn/Sr	733 ± 116	596 ± 191	0.545	>0.05	0.81

Table 4: Comparison of mean values (M±SEM) of Br, Fe, Rb, Sr, and Zn concentration (mg/L) and also Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr concentration ratio in prostate fluid of health men and patients with BPH.

M: Arithmetic Mean; SEM: Standard Error of Mean; *Wilcoxon-Mann-Whitney *U*-test.

Discussion

Comparison with published data

The mean values and all selected statistical parameters were calculated for five TE (Br, Fe, Rb, Sr, and Zn) concentrations and for four TE ratios (Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr) (Table 2). The mean of Zn concentration obtained for normal prostate fluid, as shown in Table 3, agrees well with median of means cited by other researches [26,27,32-35]. The mean of Rb concentration obtained for EPF agrees well with our data reported 37 years ago [28]. No published data referring to Br, Fe, and Sr concentrations as well as to Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios in EPF of normal prostate were found.

In the EPF samples of BPH prostate our results were comparable with published data for Zn concentrations (Table 3). No published data referring to Br, Fe, Rb, and Sr concentrations as well as to Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios in EPF samples obtained from patients with BPH were found. A number of values for Zn concentrations in normal EPF were not expressed on a wet mass basis in the cited literature. Therefore, we calculated these values using the published data for water –93.2% [36].

The range of means of Zn concentration reported in the literature for normal EPF (from 47.1 to 5185 mg/L) and for EPF of untreated BPH prostate (from 268 to 9870 mg/L) varies widely (Table 3). This can be explained by a dependence of Zn content on many factors, including age, ethnicity, mass of the gland, presence of benign prostatic hyperplasia, and others. Not all these factors were strictly controlled in cited studies. Another and, in our opinion, leading cause of inter-observer variability was insufficient quality control of results in these studies. In reported papers EPF samples were dried at high temperature or acid digestion. There is evidence that by use of these methods some quantities of TE, including Zn, are lost as a result of this treatment [37-39].

Differences in TE contents and their ratios in EPF of normal and BPH prostate

From Table 4, it is observed that in EPF of hyperplastic prostate the concentrations of Rb is 47% higher whereas the concentrations of Zn is 18% lower than levels of these trace element in EPS of normal prostate. From Table 4, it is also observed that in EPF of CP prostate the ratios of Zn/Br, Zn/Fe, and Zn/Rb are almost 20-30% lower than levels of these ratios in EPF of normal prostate, but these differences are not statistically significant.

Role of TE in the prostate function and etiology of BPH

Characteristically, elevated or deficient levels of TE and electrolytes observed in EPF are discussed in terms of their potential role in etiology of diseases. In our opinion, found changes in TE contents and their ratios in EPF of BPH prostate could be the consequence of gland disfunction. Compared to other fluids of human body, the prostate secretion has higher levels of Zn and Rb. Obtained data suggests that these TE could be involved in functional features of prostate. BPH is accompanied by a suppression of specific functional activity of prostatic cells, which leads to a small reduction in the Zn content in EPF. Why Rb content increases in the BPH prostate and how it acts on the gland are still to be fully understood. Because the values of Zn and Rb contents in EPF changed in opposite directions during enlargement of prostate the changes of the Zn/Rb ratio may be more informative. However, in our study the decrease of Zn/Rb ratio in EPF of BPH prostate (26%) was not statistically significant. Thus, this subjects needs in additional studies.

Study limitations

This study has several limitations. Firstly, analytical techniques employed in this study measure only five TE (Br, Fe, Rb, Sr and Zn) concentrations and four TE ratios (Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr) in EPF. Future studies should be directed toward using other analytical methods which will extend the list of TE investigated in EPF of normal and BPH prostate. Secondly, the sample size of BPH group was relatively small. It was not allow us to carry out the investigations of TE contents in BPH group using differentials like the grade of the disease, age, dietary habits of healthy persons and patients with BPH, and others. Despite these limitations, this study provides evidence on specific Zn and Rb level alteration in EPF and shows the necessity the need to continue TE concentration and TE ratio research of EPF in norm and BPH prostate.

Conclusion

In this work, TE measurements were carried out in the EPF samples of normal and BPH prostate using non-destructive instrumental EDXRF micro method developed by us. It was shown that this method is an adequate analytical tool for the non-destructive determination of Br, Fe, Rb, Sr, Zn concentration and ratios of these TE in the EPF samples of human prostate. It was observed significant changes in Zn and Rb contents in the fluid of hyperplastic prostate. In spite of opposite directions in changes of Zn and Rb contents in EPF of BPH prostate the alteration in level of Zn/Rb ratio was not statistically significant. In our opinion, found changes in TE contents and their ratios in EPF of BPH prostate could indicate a suppression of specific functional activity of the gland.

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Conflict of Interest

The authors have not declared any conflict of interests.

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