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

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Methods: Prostatic fluid levels of Br, Fe, Rb, Sr and Znwere prospectively evaluated in 33 patients with chronic prostatitis and also in 42 healthy males. Measurements were performed using 109Cd radionuclide-induced energy dispersive X-ray fluorescent microanalysis. The results allowed values of the Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr concentration ratios to be calculated.

Results: It was observed that in the inflamed prostates the ratios of Zn/Br, Zn/Fe, and Zn/Rb significantly decreased in a comparison with those normal prostates.

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Results: It was observed that in the inflamed prostates the ratios of Zn/Br, Zn/Fe, and Zn/Rb significantly decreased in a comparison with those normal prostates.

Conclusion: The alterations in levels of Zn/Br, Zn/Fe, and Zn/Rb in the fluid of inflamed prostates indicate involvement of these trace elements in the etiology and pathogenesis of chronicprostatitis. It is therefore supposed that the appropriate changes of the ratios of Zn/Br, Zn/Fe, and Zn/Rb in prostatic fluid samples can be used as markers of chronicprostatitis.

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I. Introduction

The prostate gland is subject to various disorders and of them chronic prostatitis (CP) is a complex disease. CP causes a range of symptoms including pain, urinary problems, such as urgency and frequency, reduced quality of life and sexual dysfunction. About 35–50% of men are reported to be affected by symptoms suggesting CP during their lifetime (1,2). Etiology of CP is not fully understood and 2treatment is frequently unsuccessful (3,4). Fragmentary epidemiological evidence indicates that risk factors such as infection, autoimmunity, inflammation, excessive amounts of tumor-related proteins, imbalance of hormones and nutrition-related variables, including some trace elements (TE) as micronutrients, may be associated with CP (5). CP is characterized by a multifactorial pathogenesis, and the condition is defined on the basis of clinical presentation rather than clear diagnostic markers or findings (6). The absence of robust and unambiguous diagnostic markers may cause the CP symptoms to overlap with those of other conditions, such as benign prostatic hyperplasia and prostate and cancer (7).

Oxidative stress has significant involvement in the pathogenesis of CP (8). Oxidative stress is a result of the imbalance between reactive oxygen species and antioxidants, including some TE, in the body that can cause tissue and organ damage. TE, besides their antioxidant properties, have many other essential physiological functions such as 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 (9,10). Besides the total amounts of individual TE, ratios of several TE should be taken into account to allow for a more reliable description of both the individual TE and health status (9,11).

In our previous studies a significant involvement of Zn, 32 Ca, Mg, Rb and some other TE in the functions of the prostate were studied. (12-22). One of the main functions of the prostate gland is the production of prostatic fluid (23). It contains a high concentration of Zn and elevated levels of Ca, Mg, Rb, and some other TE in comparison with those in serum and other fluids of the human body.

The first finding of remarkably high levels of Zn in human expressed prostatic fluid (EPF) was reported in the early 1960s (24). After analyzing EPF expressed from the prostates of 8 apparently healthy men aged 25-55 years it was found that Zn concentrations varied from 300 to 730 mg/L. After this finding several investigators have suggested that the measurement of Zn levels in EPF may be useful as a marker of abnormal prostate secretory function (25, 26). It promoted more detailed studies of the Zn concentrations in the EPF of healthy subjects and in those with different prostatic diseases, including CP (26, 27). A detailed review of these studies, reflecting the contradictions within accumulated data, was given in our earlier publication (27). Moreover, the method and apparatus for micro

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analysis of Br, Fe, Rb, Sr, and Zn in the EPF samples using energy dispersive X-ray fluorescence (EDXRF) activated by radiation from the radionuclide source 109Cd was developed by us (28).

Thus, data on changes of TE content in EPF of patients with CP are very important, because this can clarify our knowledge of CP pathogenesis and may prove useful as CP diagnostic markers. In the present study it was supposed that apart from total amounts of TE the ratios of Zn to some other TE content in EPF are likely to reflect a disturbance of prostate function. To our knowledge there are no 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 concentrations in the EPF samples obtained from apparently healthy persons and patients with CP using the 109Cd EDXRF micro method. The second aim was to evaluate the quality of these results and to compare them with published data. The last aim was to calculate the Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios and compare their values with those obtained from EPF samples from normal and inflamed prostate glands. 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 75 national research committee and with the 1964 Helsinki declaration and its later amendments, or with comparable ethical standards.

II. Material and Methods

Specimens of EPF were obtained from 42 men with apparently normal prostates (mean age ± Standard Deviation - 54±13 years, range 31-75 years) and from 33 males with CP (mean age 50±9 years, range 37-65 years) in the Urological Department of the Medical Radiological Research Centre using standard rectal massage procedure. The diagnosis of CP was made by qualified urologists and in all cases the CP diagnosis was confirmed by clinical examination and by cytological and bacteriological investigations of the EPF samples. Subjects were asked to abstain from sexualinter course for three days preceding the procedure Specimens of EPF were obtained in sterile containers which were appropriately labeled. Twenty μL (microliters) of fluid were taken in duplicate by micropipette from every specimen for TE analysis, while the rest of the fluid was used for cytological and bacteriological investigations. One 20 μL sample of the EPF was dropped on a 11.3 mm diameter disk made of thin, ash-free filter paper fixed on pieces of Scotch tape pieces and dried in an exsiccator at room temperature. Then the dried sample was covered with a 4 mm Dacron film and centrally pulled onto a Plexiglas cylindrical frame (28).

To determine concentration of the TE by comparison with known standard, aliquots of solutions of commercial, chemically pure compounds were used for calibration (29). 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 Materials (CRM) ten sub-samples of the powdered CRM IAEA H-4 (animal muscle) were analyzed to estimate the precision and accuracy of results. Every CRM sub-sample 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 11.3mm 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 Scotch tape surface restricted by the 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 mm Dacron film. Before the sample was applied, pieces of Scotch tape and Dacron film were weighed using an analytical balance. They were reweighed after the sample had been placed inside to determine the sub- sample mass precisely.

The facility for the radionuclide-induced energy dispersive X-ray fluorescence included an annular 109Cd source with an activity of 2.56 GBq, ASi (Li) detector with an electric cooler and a portable multi-channel analyzer combined with a PC, comprised the detection system. Its resolution was 270eV at the 6.4 keV line. The facility functioned as follows. Photons with energy 22.1 keV from the 109Cd source arrive at the surface of the specimen inducing the fluorescent Ka X-rays from TE. The fluorescence reaches the detector after passing through a 10 mm diameter collimator. Then the X-ray's arrival is recorded. The duration of the measurements of Br, Fe, Rb, Sr, and Zn concentration for each sample was 60 min. The intensity of Ka-line of Br, Fe, Rb, Sr, and Zn for EPF samples and standards was estimated from a calculation the total area under the corresponding photo peak in the spectra.

All EPF samples for EDXRF were prepared in duplicate and mean values of TE contents were used in the 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 the Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios in the EPF of normal and CP prostates. The difference in the results between the two groups of samples (normal prostate and CP) was evaluated by the parametric Student's t-test and non-parametric Wilcoxon-Mann-Whitney U-test.

III. 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.

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

Element	Certified values			This work
	Mean	95% confidence interval	Type	M±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

Mean – arithmetical mean, SD – standard deviation, C- certified values, N – non-certified values.

The contents of four TE (Br, Fe, Rb, and Zn) were determined. These TE have certified values for the CRM IAEA H-4 (animal muscle) (Table 1). Mean values (M±SD) for Br, Fe, Rb, and Zn were in the range of the 95% confidence interval. Good agreement of the TE contents analyzed by 109Cd 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.

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 CP prostates.

The comparison of our results with published data for Br, Fe, Rb, Sr, and Zn concentrations and also for the Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios in EPF of normal and CP prostate. [26, 27, 30-32] is shown in Table 3.

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

Discussion

The mean values and all selected statistical parameters were calculated for five TE (Br, Fe, Rb, Sr, Zn) concentrations and four TE ratios (Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr) ratios (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, 30-32). The mean of Rb concentration obtained for EPF agrees well with our data reported 37 years ago (26). No published data referring to Br, Fe, and Sr concentrations as well as to the ratios Zn/Br, Zn/Fe, Zn/Rb, Zn/Sr ratios in EPF of normal prostates were found.

Table 2: Some basic statistical parameters of Br, Fe, Rb, Sr, and Zn concentration (mg/L) and Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr concentration ratios in prostate fluid of healthy men and patients with chronic prostatitis

Condition of prostate	Element or ratio	M	SD	SEM	Min	Max	Median	Per. 0.025	Per. 0.975
Norm 31-75 years n=42	Br	2.81	2.88	0.57	0.490	8.53	1.26	0.496	8.53
	Fe	8.29	7.49	1.37	1.27	39.8	7.47	1.29	22.9
	Rb	1.15	0.51	0.09	0.376	2.45	1.05	0.424	2.38
	Sr	1.17	0.83	0.16	0,400	3.44	1.15	0,400	3.19
	Zn	559	204	32	253	948	549	254	941
	Zn/Br	624	603	118	43	1882	374	48	1882
	Zn/Fe	117	96	18	13.0	343	77.0	17.0	343
	Zn/Rb	628	369	67	119	1612	534	196	1513
	Zn/Sr	750	539	104	155	2321	619	167	2015
Prostatitis 37-65 years n=33	Br	3.35	2.64	0.69	0.120	9.85	2.98	0.201	8.73
	Fe	10.9	9.6	2.3	3.85	41.9	6.97	4.06	35.6
	Rb	2.32	1.13	0.30	0.730	4.54	1.75	0.935	4.34
	Sr	1.57	1.36	0.79	0.210	2.93	1.58	0.279	2.86
	Zn	382	275	48	62.0	1051	295	75.0	950
	Zn/Br	129	96	32	14.1	322	103	20.2	298
	Zn/Fe	35.9	20.6	5.3	7.03	66.3	33.7	9.12	66.0
	Zn/Rb	175	101	29	41.3	381	154	48.8	367
	Zn/Sr	484	732	422	34.6	1329	88.2	37.3	1267

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.

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

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	-	-	-	2.81±2.88
	Fe	-	-	-	8.29±7.49
	Rb	1.11 (1)	1.11±0.57 (15) [26]	1.11±0.57 (15) [26]	1.15±0.51
	Sr	-	-	-	1.17±0.83
	Zn	453 (19)	47.1(-) [30]	5185±3737 (10) [31]	559±204
	Zn/Br	-	-	-	624±603
	Zn/Fe	-	-	-	117±96
	Zn/Rb	-	-	-	628±369
	Zn/Sr	-	-	-	750±539
Prostatitis	Br	-	-	-	3.35±2.64
	Fe	-	-	-	10.9±9.6
	Rb	2.26 (1)	2.26±1.28 (18) [26]	2.26±1.28 (18) [26]	2.32±1.13
	Sr	-	-	-	1.57±1.36
	Zn	222 (7)	88.9 (29) [32]	564±239 (10) [31]	382±275
	Zn/Br	-	-	-	129±96
	Zn/Fe	-	-	-	35.9±20.6
	Zn/Rb	-	-	-	175±101
	Zn/Sr	-	-	-	484±732

M - Arithmetic mean, SD – Standard deviation, (n)* – Number of all references, (n)** - Number of samples.

Table 4: Comparison of mean values (M±SEM) of Fe, Zn, Br, Rb, and Sr concentrations (mg/L) as well as of Zn/Br, Zn/Fe, Zn/Rb, and Zn/Sr ratios in prostate fluid of healthy men and patients with chronic prostatitis

Element or ratio	Age groups				Ratios
	Norm	Prostatitis	Student t-test p ≤	U-test* p	Prostatitis to Norm
Br	2.81±0.57	3.35±0.69	0.546	>0.05	1.19
Fe	8.29±1.37	10.9±2.3	0.342	>0.05	1.31
Rb	1.15±0.09	2.32±0.30	0.0021	<0.01	2.02
Sr	1.17±0.16	1.57±0.79	0.662	>0.05	1.34
Zn	559±32	382±48	0.0030	<0.01	0.68
Zn/Br	624±118	129±32	0.00037	<0.01	0.21
Zn/Fe	117±18	35.9±5.3	0.00016	<0.01	0.31
Zn/Rb	628±67	175±29	0.0000004	<0.01	0.28
Zn/Sr	750±104	484±422	0.596	>0.05	0.65

M – Arithmetic mean, SEM – Standard error of mean, *Wilcoxon-Mann-Whitney U-test, bold – Significant difference (p≤0.05).

In the EPF samples of CP prostates 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 CP, were found.

In the cited literature a number of values for Zn concentrations in normal EPF were not expressed on a wet mass basis. Therefore, we calculated these values using the published data for water –93.2% (33).

From Table 4, it is observed that in the EPF of CP prostates the ratios of Zn/Br, Zn/Fe, and Zn/Rb are almost 5, 3, and 4 times, respectively, lower than levels of these ratios in EPF of normal prostates.

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 CP prostate (from 88.9 to 564 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. These factors were not controlled in the cited studies. Another and, in our opinion, leading cause of inter observer variability was insufficient quality control of results in these studies. In many reported papers EPF samples were dried at high temperature or with acid digestion. There is evidence that by use of these treatment methods some quantities of trace elements, including Zn, are lost as a result of this treatment (34-36).

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, abnormal levels of some TE and their ratios in EPF of CP prostate could be the consequence of inflammation. Compared to other fluids of the human body, the prostate secretion contains higher levels of Zn and some other TE. These data suggest that these TE could be involved in functional aspects of the prostate. Inflammation is accompanied by a suppression of specific functional activities of prostatic cells, which leads to a small reduction in the Zn content in EPF. Why Br, Fe, Sr, and particularly Rb content increase in the EPF of CP prostate and how it acts on the gland are still to be fully understood.

Our findings show that the concentration of Br, Fe, Sr, and particularly Rb increased whereas the concentration of Zn is somewhat decreased in the EPF of CP prostate as compared to their levels in EPF of normal prostates (Table 4). Our present results have formed the basis for a new method for diagnosis of CP, the essence of which will be evaluation of the ratios of TE content, which in EPF have changed in different directions during prostatic inflammation. In other words, it is plausible to assume that levels of such TE ratios in EPF as Zn/Br, Zn/Fe, and Zn/Rb in EPF can be used as CP markers.

This study has several limitations. Firstly, analytical techniques employed in this study measure only five TE (Br, Fe, Rb, Sr and Zn) concentrations in EPF. Future studies should be directed toward using additional analytical methods which will extend the list of TE investigated in the EPF of normal and inflamed prostates. Secondly, the sample size of CP group was relatively small. It did not allow us to carry out the investigations of TE contents in a sufficiently large CP group, which could investigate differentials like age, dietary habits of healthy persons and patients with CP, and other patient characteristics. Despite these limitations, this study provides some unequivocal evidence on inflammation -specific Zn/Br, Zn/Fe, and Zn/Rb ratio alterations in the EPF and shows the necessity to extend TE ratio research of EPF in normal prostates and prostatic diseases, along the lines we have indicated.

IV. Conclusion

In this work, TE measurements were carried out in the EPF samples of normal and CP prostates using the 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 also ratios of some of these TE in the EPF samples of human prostates. It was observed that in the EPF of CP prostates the ratios of Zn/Br, Zn/Fe, and Zn/Rb decreased in a comparison with those in the EPF of normal prostates. In our opinion, the observed alterations in levels of Zn/Br, Zn/Fe, and Zn/Rb ratios in the EPF of inflamed prostates demonstrate an involvement of these trace elements in the etiology and pathogenesis of CP. So it is presumed that the changes in the Zn/Br, Zn/Fe, and Zn/Rb ratios in the EPF samples can be used as markers of the presence of CP.

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