RESEARCH ARTICLE

Trace Elements of Expressed Prostatic Secretions as a Source for Biomarkers of Prostate Cancer

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ABSTRACT

Background: Prostate cancer (PCa) is an internationally important health problem of the man, particularly in developed countries. The aim of this exploratory study was to evaluate whether significant changes in the levels of zinc (Zn) and some other trace elements of prostatic fluid exist in the malignantly transformed prostate. **Methods:** Prostatic fluid levels of Br, Fe, Rb, Sr, and Zn were prospectively evaluated in 24 patients with PCa and 38 healthy male inhabitants. Measurements were performed using ^{109}Cd radionuclide-induced energy dispersive X-ray fluorescent microanalysis. Prostatic fluid samples were divided into two portions. One was used for morphological study while the other was intended for trace element analysis. **Results:** Mean values ± standard error of means for concentration (mg/L) of trace element in the prostatic fluid of normal prostate were: Br 2.86 ± 0.59, Fe 8.30 ± 1.42, Rb 1.16 ± 0.10, Sr 1.27 ± 0.17, and Zn 598 ± 34. The contents of Rb and Zn were significantly lower (approximately 2 and 10 times, respectively) in the fluid of cancerous prostate compared with those in fluid of normal prostate. **Conclusions:** There are significant changes in trace element contents and their relationships in the fluid of malignantly transformed prostate. The decrease in levels of Zn and Rb in the fluid of cancerous prostate might demonstrate involvement of these trace elements in etiology and pathogenesis of malignant prostate tumors. It was supposed that the changes of Zn and Rb levels in the prostatic fluid can be used as tumor markers.

Key words: Energy-dispersive X-ray fluorescent analysis, prostate cancer, prostatic fluid, trace elements

INTRODUCTION

Globally, prostate cancer (PCa) is the sixth most common cancer and the first most common cancer in males in many industrialized countries of Europe.[1-5] The American Cancer Society declares PCa as the most common cancer in males and the second leading cause of cancer death.[6] Moreover, PCa is the leading cancer in terms of incidence and mortality in men from Africa and the Caribbean.[7] PCa in China has also become a major public health concern.[8]

Prostate specific antigen screening for PCa appears to have produced considerable over-diagnosis and overtreatment.[9] Overtreatment is likely to continue as a patient-driven phenomenon unless better non-invasive tests for the detection and stratification of PCa will be developed.

Although the etiology of PCa is unknown, several risk factors including such micronutrients as calcium (Ca) and zinc (Zn) have been well identified.[10-13] Trace elements have 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 and carcinogenic) properties of trace elements depend on tissue-specific need or tolerance, respectively.[14] Excessive accumulation or an imbalance of the trace elements may disturb the cell functions and may result in cellular degeneration, death or malignant transformation.[14-16]

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In our previous studies, significant involvement of Zn and some trace element in the function of prostate was observed.[17-27] Moreover, it was found that intracellular Zn and Ca excess is one of the main factors in the etiology of PCa.[28,29] One of the main functions of the prostate gland is a production of prostatic fluid[30] with an extremely high concentration of Zn and some other chemical elements. The first finding of the remarkable high level of Zn concentration in human expressed prostatic fluid (EPF) was reported at the beginning of the 1960s.[31] Analyzing EPF expressed from prostate of 8 apparently healthy men aged 25–55 years it was found that Zn concentration varied in the 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.[32,33] It promoted a more detailed study of Zn concentration in EPF of healthy subjects and those with different prostate diseases, including PCa.[33,34] A detailed review of these studies, reflecting the contradictions within accumulated data, was given in our earlier publication.[34]

In the present study, it was supposed by us that apart from Zn the levels of some other trace elements in EPF have to reflect a functional disintegration of the prostate. Thus, this work had four aims. The first one was to present the design of the method and apparatus for microanalysis of Br, Fe, Rb, Sr, and Zn in the EPF samples using energy dispersive X-ray fluorescence (EDXRF) with radionuclide source ^{109}Cd. The second aim was to assess the Br, Fe, Rb, Sr, and Zn concentration in the EPF samples received from patients with normal and cancerous prostate gland. The third aim was to evaluate the quality of the obtained results and to compare the obtained results with published data. The last aim was to compare the concentration of Br, Fe, Rb, Sr, and Zn and intercorrelations of these trace elements in EPF samples of normal and cancerous prostate gland.

MATERIALS AND METHODS

Specimens of EPF were obtained from 38 men with apparently normal prostates (mean age ± standard deviation - 59 ± 11 years and range 41–82 years) and from 24 patients with PCa (mean age 65 ± 10 years and range 47–77 years) by qualified urologists in the Urological Department of the Medical Radiological Research Center using standard rectal massage procedure. In all cases, the diagnosis has been confirmed by clinical examination and in cases of PCa additionally 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. Twice 20 μL of fluid were taken by micropipette from every specimen for trace element analysis, while the rest of the fluid was used for cytological and bacteriological investigations. The chosen 20 μL of the EPF 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 desiccator at room temperature. Then, the dried sample was covered with 4 μm Dacron film and centrally pulled onto a Plexiglas cylindrical frame [Figure 1].

To determine concentration of the elements by comparison with a known standard, aliquots of solutions of commercial, chemically pure compounds were used for device calibration.[35] The standard samples for calibration were prepared in the same way as the samples of prostate fluid. Since there was no available liquid certified reference material (CRM), 10 sub-samples of the powdery 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 11.3 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.

The facility for radionuclide-induced EDXRF included an annular ^{109}Cd source with an activity of 2.56 GBq, Si(Li) detector with electric cooler and portable multi-channel 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

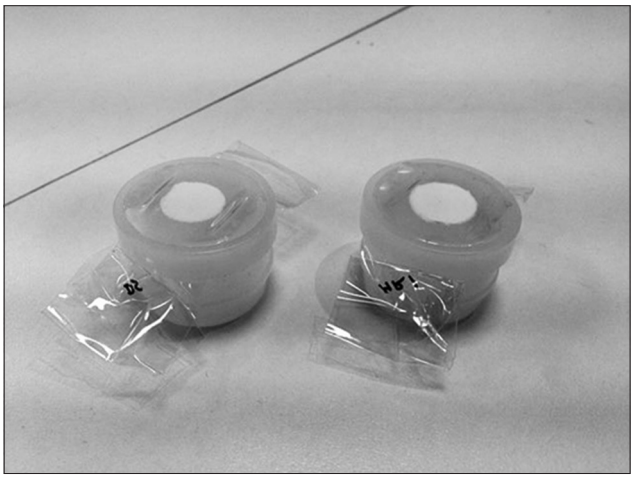

Figure 1: The dried samples of prostate fluid on filter paper disks fixed on the Scotch tape pieces centrally pulled onto a Plexiglas cylindrical frame

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 was 10 min. 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 the calculation basis of the total area of the corresponding photopeak in the spectra.

All EPF samples for EDXRF were prepared in duplicate and mean values of trace element 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 (SEM), minimum and maximum values, median, and percentiles with 0.025 and 0.975 levels was calculated for trace element concentrations in EPF of the normal and cancerous prostate. The difference in the results between two groups of samples (normal prostate and PCa) was evaluated by the parametric Student's *t*-test and non-parametric Wilcoxon-Mann–Whitney U-test. For the estimation of the Pearson correlation coefficient between different pairs of the trace element concentration in the prostate fluid of health men and patients with PCa, the Microsoft Office Excel program was also used.

RESULTS

Table 1 depicts our data for 5 trace elements in 10 sub-samples of CRM IAEA H-4 (animal muscle) and the certified values of this material.

Table 2 presents certain statistical parameters (arithmetic mean, standard deviation, SEM, minimal and maximal values, median, and percentiles with 0.025 and 0.975 levels)

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)

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

Mean: Arithmetical mean, SD: Standard deviation, C: Certified values, N: Non-certified values. EDXRF: Energy dispersive X-ray fluorescence, Zn: Zinc

of the Br, Fe, Rb, Sr, and Zn concentrations in EPF of normal and cancerous prostate.

The comparison of our results with published data for Br, Fe, Rb, Sr, and Zn concentrations in EPF of the normal and cancerous prostate[33,34,36-38] is shown in Table 3.

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

Table 5 contains the results of inter-element correlation calculations (values of *r* - coefficient of correlation) including all trace elements identified in this work.

DISCUSSION

Good agreement of the Fe, Zn, Br, Rb, and Sr contents analyzed by ^{109}Cd radionuclide-induced EDXRF with the certified data of CRM IAEA H-4 [Table 2] indicates an acceptable accuracy of the results obtained in the study of trace elements of the prostate fluid presented in Tables 2-5.

The mean values and all selected statistical parameters were calculated for 5 trace elements (Br, Fe, Rb, Sr, and Zn) of trace element concentrations [Table 2]. The concentrations of Br, Fe, Rb, Sr, and Zn were measured in all or a major portion of EPF samples of normal and cancerous prostate.

The mean of Zn concentration obtained for normal prostate fluid, as shown in Table 3, agrees well with a median of means cited by other researches.[32,36-38] The mean of Rb concentration obtained for EPF agrees well with our data reported 37 years ago.[33] No published data referring to Br, Fe, and Sr concentrations in normal EPF were found.

In the EPF samples of cancerous prostate our results were comparable with published data for Zn concentrations [Table 3]. No published data referring to Br, Fe, Rb, and Sr concentrations in EPF samples obtained from patients with PCa 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 content in EPF - 93.2%.[39]

From Table 4, it is observed that in EPF of the cancerous prostate the concentrations of Rb and Zn are almost 2 ($P < 0.00019$) and 10 ($P < 0.000001$) times, respectively, lower than in EPS of normal prostate.

Interelement correlations between trace elements are significantly altered in EPF of the cancerous prostate as compared to their relationships in EPF of normal prostate

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

Condition	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
PCa	Br	4.51	7.19	2.27	0.697	24.3	2.08	0.704	20.4
47–77 years	Fe	21.7	28.8	8.7	7.70	107	13.9	7.70	86.8
n=24	Rb	0.53	0.38	0.11	0.013	1.39	0.422	0.024	1.26
	Sr	1.70	2.15	0.76	0.230	6.83	0.872	0.275	5.95
	Zn	62.0	98.3	20.1	2.82	371	21.6	3.43	358

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, PCa: Prostate cancer, Zn: Zinc

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

Condition	El	Published data [Reference]			This workresults
		Median of means (*n*)*	Minimum of means Mean or Mean±SD, (*n*)**	Maximum of means Mean±SD, (*n*)**	Mean±SD
Norm	Br	-	-	-	2.86±2.93
	Fe	-	-	-	8.30±7.62
	Rb	2.26 (1)	1.11±0.57 (15) [33]	2.35±1.85 (11) [33]	1.16±0.52
	Sr	-	-	-	1.27±0.84
	Zn	453 (19)	47.1(-) [36]	5185±3737 (10) [37]	598±207
PCa	Br	-	-	-	4.51±7.19
	Fe	-	-	-	21.7±28.8
	Rb	1.11 (1)	1.11±0.57 (15) [33]	1.11±0.57 (15) [33]	0.53±0.38
	Sr	-	-	-	1.70±2.15
	Zn	65.4 (6)	34.7±34.6 (13) [34]	722 (3) [38]	62.0±98.3

El: Element, M: Arithmetic mean, SD: Standard deviation, *n**: Number of all references, *n***: Number of samples, PCa: Prostate cancer, Zn: Zinc

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

Element	Norm and PCa groups				Ratios
	Norm	PCa	Student's *t*-test *P*≤	*U*-test* *P*	PCa to Norm
Br	2.86±0.59	4.51±2.27	0.498	>0.05	1.58
Fe	8.30±1.42	21.7±8.7	0.157	>0.05	2.61
Rb	1.16±0.10	0.53±0.11	**0.00019**	**<0.01**	0.46
Sr	1.27±0.17	1.70±0.76	0.598	>0.05	1.34
Zn	598±34	62.0±20.1	**0.000001**	**<0.01**	0.104

M: Arithmetic mean, SEM: Standard error of mean, *Wilcoxon-Mann–Whitney U-test, **Bold:** Significant difference (*P*≤0.05), PCa: Prostate cancer, Zn: Zinc

[Table 5]. In EPF of cancerous prostates, some significant correlations between trace elements found in the EPF of the control group are no longer evident, but other correlations arise. For example, in the healthy prostate of

Table 5: Intercorrelations of pairs of the trace element concentration in the prostate fluid of health men and patients with PCa (*r* - coefficient of correlation)

Tissue	Element	Br	Fe	Rb	Sr	Zn
Norm	Br	1.0	0.714[c]	0.178	0.172	−0.535[c]
41–82 years	Fe	0.714[c]	1.0	0.148	0.410[b]	−0.241
n=38	Rb	0.178	0.148	1.0	−0.131	−0.097
	Sr	0.172	0.410[b]	−0.131	1.0	0.069
	Zn	−0.535[c]	−0.241	−0.097	0.069	1.0
PCa	Br	1.0	0.856[b]	−0.472	0.962[c]	0.291
47–77 years	Fe	0.856[b]	1.0	0.684[a]	0.921[c]	0.314
n=24	Rb	−0.472	0.684[a]	1.0	−0.503	−0.091
	Sr	0.962[c]	0.921[c]	−0.503	1.0	0.387
	Zn	0.291	0.314	−0.091	0.387	1.0

Statistically significant values with: [a]$P \leq 0.05$, [b]$P \leq 0.01$, [c]$P \leq 0.001$. PCa: Prostate cancer

men, Zn concentration in EPF has significant ($P < 0.01$) inverse correlation with Br [Table 5]. Thus, if we accept the relationships of trace element concentrations in EPF of males in the control group as a norm, we have to conclude that with a malignant transformation the relationships between trace elements in EPF significantly changed. No published data referring to correlations between trace elements concentrations in EPF of the normal and cancerous prostate were found.

The range of means of Zn concentration reported in the literature for normal EPF (from 47.1 to 5185 mg/L) and EPF of untreated cancerous prostate (from 34.7 to 722 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, the cancer stage, and others. Not all these factors were strictly controlled in cited studies. Another and, in our opinion, leading cause of interobserver variability was insufficient quality control of results in these studies. In many reported that papers EPF samples were dried at high temperature or acid digestion. There is evidence that by use of these methods some quantities of trace elements, including Zn, are lost as a result of this treatment.[40-42]

Characteristically, elevated or deficient levels of trace elements and electrolytes observed in EPF of the cancerous prostate are discussed in terms of their potential role in the initiation, promotion, or inhibition of PCa. In our opinion, abnormal levels of many trace elements in EPF of cancerous prostate could be the consequence of malignant transformation. Compared to other fluids of the human body, the prostate secretion has higher levels of Zn and some other trace elements. These data suggest that these elements could be involved in the functional features of the prostate. Malignant transformation is accompanied by a loss of tissue-specific functional features, which leads to a significant reduction in the contents of elements associated with functional characteristics of the human EPF (Zn and, probably, and Rb).

Our findings show that the concentration of Rb and Zn is significantly lower in EPF of the cancerous prostate as compared to their concentrations in EPF of normal prostate [Table 4]. Thus, it is plausible to assume that levels of these trace elements in EPF can be used as tumor markers. However, this subjects needs in additional studies.

This study has several limitations. First, analytical techniques employed in this study measure only five trace element (Br, Fe, Rb, Sr, and Zn) concentrations in EPF. Future studies should be directed toward using other analytical methods which will extend the list of chemical elements investigated in EPF of the normal and cancerous prostate. Second, the sample size of PCa group was relatively small. It was not allow us to carry out the investigations of trace element contents in PCa group using differentials such as histological types of tumors, stage of disease, and dietary habits of healthy persons and patients with PCa. Despite these limitations, this study provides evidence on cancer-specific Rb and Zn level alteration in EPF and shows the necessity the need to continue chemical element research of EPF in norm and prostatic diseases.

CONCLUSIONS

In this work, trace elemental measurements were carried out in the EPF samples of the normal and malignant 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, and Zn concentration in the EPF samples of human prostate. It was observed that in the EPF of cancerous prostate contents of Zn and Rb

significantly decrease in comparison with those in the EPF of normal prostate. In our opinion, the decrease in levels of Zn and Rb in the EPF of cancerous prostate might demonstrate involvement of these trace elements in etiology and pathogenesis of malignant prostate tumors. It was supposed that the changes of Zn and Rb levels in the EPF samples can be used as tumor markers.

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