International Urology and Nephrology 28 (5), pp. 687–694 (1996)

Zinc Concentration in Human Prostatic Fluid: Normal, Chronic Prostatitis, Adenoma and Cancer

V. YE. ZAICHICK, T. V. SVIRIDOVA, S. V. ZAICHICK
Medical Radiological Research Centre, Obninsk, Kaluga Region, Russia

(Accepted June 18, 1996)

Radionuclide induced energy dispersive X-ray fluorescence was used to estimate zinc content in prostatic fluid in normal, chronic prostatitis, adenoma and cancer cases. Groups of patients suffering from chronic prostatitis, adenoma and malignant tumours consisting of 28, 28 and 13 men, respectively, were examined. The control group included 22 healthy volunteers. Expressed prostatic fluid was obtained by digital rectal massage. The zinc concentration of intact prostatic fluid was 590±45 (SE) μg/ml. Almost no difference was found between the zinc concentration for chronic prostatitis and for adenoma, and those for normal levels being 455±60 (SE) and 540±50 (SE) μg/ml, respectively. Prostatic neoplasm resulted in a significant decrease of zinc secretion, with the concentration averaging 34.7±9.6 μg/ml, $p<0.000001$.

As long ago as the early 20th century it was known that prostatic zinc concentration was many times higher than that in other body tissues [2]. Prostatic zinc accumulation was connected with the secretory function of the prostate. The results for zinc in healthy human prostatic fluid were first published in 1962 [17]. It was shown that zinc concentration of prostatic fluid ranged between 3900 and 9800 μg/g in a dry sample, averaging 7200±1900 (SD) μg/g. This value was approximately 10-fold higher than zinc in dry prostatic tissue.

Later, zinc in healthy human prostatic fluid was estimated by several investigators [7, 13, 14, 18]. In spite of a relatively small number of papers on the subject, their data correlate well with each other.

The zinc concentrations present in prostatic diseases differ greatly from the normal level. For a hyperplastic gland, zinc significantly increases. In contrast to that, in a tumour the concentration averages several times less than the values typical of normal prostatic tissue [8, 19]. The difference found between zinc concentrations in adenoma and cancer stimulated the search for new methods of differential diagnosis for these diseases [12]. However, putting such diagnostic approaches into practice required tissue puncture biopsies [5]. Prostatic fluid is much more available for study and can be obtained with no prostatic damage. Information about zinc concentrations in prostatic fluid in different prostatic diseases is of obvious interest not only to more profoundly

VSP, Utrecht
Akadémiai Kiadó, Budapest

understand the aetiology and pathogenesis of prostatic diseases, but also for their diagnosis. However, information about fluid zinc in prostatic diseases is rather poor and greatly contradictory [6, 14, 21].

In the present paper we estimated the zinc content in the prostatic fluid of healthy men and of patients suffering from chronic prostatitis, adenoma, and prostatic neoplasm.

Materials and methods

All patients examined (n=69) were treated at the Department of Urology of the Medical Radiological Research Centre (MRRC), Obninsk. In each case the diagnosis was verified by clinical and morphological evidence, obtained if necessary, by examinations of biopsy and resected materials (Department of Morbid Anatomy of MRRC). The 28 patients suffering from chronic prostatitis were aged 25–72, averaging 49.3±2.4 (SE). The age of 28 patients with prostatic adenoma ranged 52–75, averaging 63.7±1.1 (SE). The group of patients with prostatic malignant tumours consisted of 13 men aged 47–81, averaging 67.1±3.0 (SE). The control group of 22 healthy volunteers were aged 22–75, averaging 48.9±3.6 (SE).

Expressed prostatic fluid was conventionally obtained by digital rectal massage. Such fluid specimens are relatively free of contamination by spermatozoa, urine or vesicular fluid [15]. Twenty μl of secretion were taken in a capillary tube from every specimen to analyse it for zinc, while the rest of the fluid was studied cytologically and bacteriologically. The chosen 20 μl of secretion were dropped onto a special backing, the bottom of which was made of dacron film 4 μm thick. Then drops were dried in a vacuum.

Radionuclide induced energy dispersive X-ray fluorescence (XRF) was used to analyse zinc. The device consisted of an annular ^{109}Cd radionuclide source with an activity of 2 GBq, a 25 mm^2 Si(Li) detector and a multichannel analyser. The device provided a resolution of 270 eV at the 5.9 KeV line. The device functioned the following way. Photons with the 22.1 KeV ^{109}Cd source were sent to the surface of a specimen inducing the fluorescence Kα X-ray of zinc at about 8.6 KeV. The fluorescence irradiation got the detector through a collimator being recorded. The relative method was used to estimate zinc according to the intensity of the Kα fluorescence irradiation. IAEA reference material, H-4 (animal muscle), containing a certified value of zinc, was used as a standard [20].

The 10-minute exposure made it possible to determine zinc in most fluid specimens with a total error of not more than 5%. Each specimen was measured at least three times. The results obtained were averaged. The results were statistically analysed using both the parametric Student *t*-test and the non-parametric Kolmogorov–Smirnov test.

Results

Prostatic fluid zinc concentration is given in Fig. 1. The small number of observations did not permit us to estimate the distribution law of zinc concentration in prostatic fluid with statistical significance in each male group examined. This uncertainty existing for the distribution law of the studied parameter made it necessary to calculate some other statistical characteristics in addition to the arithmetical mean.

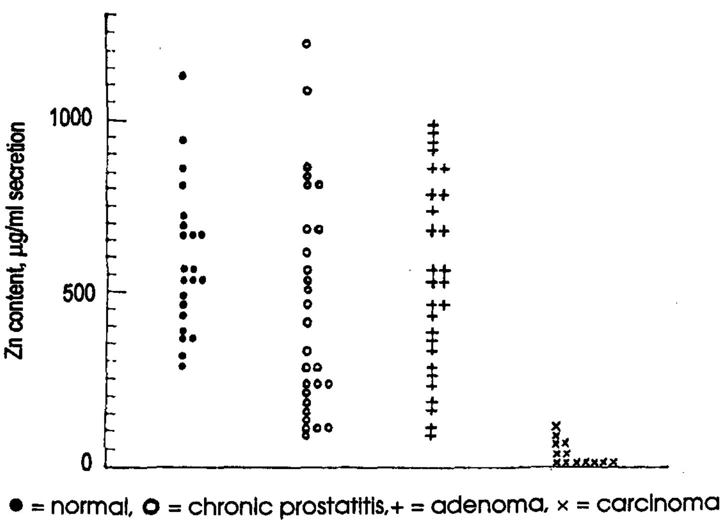

Fig. 1. Prostatic fluid zinc concentration

Since there was a sufficient number of men aged below 50 in the control group and in the group of patients with chronic prostatitis, it seemed possible to evaluate the age influence on prostatic fluid zinc concentration. The control group consisted of 10 men aged 50 or younger, averaging 32.6±2.9, and 12 men above 50, averaging 62.4±2.2. A group of patients suffering from chronic prostatitis included 17 men younger than 50, averaging 40.0±2.0, and 11 men older than 50, averaging 62.7±1.3. Thus, the age difference between these age groups exceeded 20 years on the average. Nevertheless, we have not found any difference in zinc concentration between the groups studied (Table 1).

No dependence of zinc concentration on age made it possible to unite all the control group and chronic prostatitis data. The results of zinc secretion concentration for normal prostate, chronic prostatitis, adenoma and cancer are presented in Tables 2 and 3. Secretion moisture content was determined by weighing secretion specimens before and after drying (Table 4).

Table 1
Zinc content of prostatic fluid in healthy men and patients with chronic prostatitis aged 50 and younger and 50 and older

	Normal				Chronic prostatitis			
	μg/g dry tissue		μg/ml		μg/g dry tissue		μg/ml	
	≤50	>50	≤50	>50	≤50	>50	≤50	>50
n	10	12	10	12	17	11	17	11
Mean	5950	6090	554	620	4780	4500	460	449
±SD	2130	1800	180	235	3010	3050	297	360
±SE	670	520	56	68	730	920	72	108
Median	5530	6160	554	603	4670	4730	402	340
Geometric mean	5610	5830	528	582	3790	3400	362	321
Min	3408	2969	314	291	798	1003	76.2	100
Max	9203	9602	860	1118	10,990	10,500	1077	1209
Student *t*-test	NS		NS		NS		NS	
Kolmogorov–Smirnov test	NS		NS		NS		NS	

NS: not significant

Table 2
Zinc content of fresh prostatic fluid (μg/ml secretion)

	n	Mean	±SE	±SD	Median	Geometric mean	Min–Max
Normal	22	590	45	210	550	556	291 –1118
Chronic prostatitis	28	455	60	317	370	345	76.2–1209
Adenoma	28	540	50	270	530	450	86.0– 977
Cancer	13	34.7	9.6	34.6	21.4	17.3	2.8– 101

Table 3
Zinc content of dried prostatic fluid (μg/g dry mass)

	n	Mean	±SE	±SD	Median	Geometric mean	Min–Max
Normal	22	6020	410	1920	5850	5710	2970 – 9600
Chronic prostatitis	28	4670	560	2970	4715	3630	798 –10,990
Adenoma	28	5450	520	2770	5210	4525	581 – 9870
Cancer	13	241	64	230	160	125	20.9– 633

Table 4
H_2O content of prostatic fluid (%)

	n	Mean	±SE	±SD	Median	Geometric mean	Min–Max
Normal	22	90.2	0.3	1.6	90.2	90.2	85.2–92.8
Chronic prostatitis	28	90.6	0.3	1.7	90.2	90.8	86.5–96.5
Adenoma	28	90.2	0.3	1.7	90.1	90.2	88.3–94.2
Cancer	13	86.7	1.1	4.0	85.1	86.7	81.9–93.9

Table 5
Confidence intervals of difference between concentrations of zinc and H_2O in prostatic fluid for cancer

Groups compared	t-test			Non-parametric test		
	Zinc µg/g dry mass	Zinc µg/ml	H_2O	Zinc µg/g dry mass	Zinc µg/ml	H_2O
Normal	<0.000001	<0.000001	<0.02	<0.000001	<0.000001	<0.05
Chronic prostatitis	<0.000001	<0.000001	<0.01	<0.000001	<0.000001	<0.03
Adenoma	<0.000001	<0.000001	<0.02	<0.000001	<0.000001	<0.05

In spite of a slight decreasing tendency in the mean values of secretion zinc concentration for chronic prostatitis and adenoma when compared with normal levels, the available differences have not been statistically confirmed by either the parametrical or non-parametrical tests. Nor does the secretion moisture content in chronic prostatitis and adenoma differ from the normal value.

The zinc concentration of prostatic fluid for neoplasm was much lower on the average than that for normal, chronic prostatitis or adenoma. The decrease was statistically confirmed by both the parametrical and non-parametrical tests. Secretion moisture content for neoplasm was also lower (Table 5).

Discussion

In the present study both mean values and ranges of zinc concentration values in prostatic fluid obtained in healthy men correlate well with previous data (Table 6).

Zinc concentration of prostatic fluid in healthy men aged 22–75 does not depend on age. This conclusion is also confirmed by the data of Fair and Cordonnier who analysed secretion in 88 men divided into three age groups: 20–39, 40–59 and 60–79 [7]. In addition, we have found no age dependence of fluid zinc content in men suffering from chronic prostatitis.

Table 6
Prostatic fluid zinc in healthy men (reference data)

Author	Year	Method	n	Age Mean (range)	Zinc (μg/ml)
Mackenzie et al. [17]	1962	XRF	8	36.6 (25–55)	706±186 (SD)*
Anderson, Fair [1]	1976	AAS	15	49.5 (30–74)	352± 49 (SE)
Fair, Cordonnier [7]	1978	AAS	63	52 (24–76)	455± 22 (SE)
Homonnai et al. [13]	1978	AAS	12		335± 13 (SE)
Marmar et al. [18]	1980	AAS	33		451±215 (SD)
Kavanagh [16]	1985	AAS	152		590±220 (SD)
Own results		Energy dispersive XRF	22	48.9 (22–75)	590±210 (SD)

* Re-count has made proceeding from the 90.2% water fluid content
AAS – atomic absorption spectrometry
XRF – X-ray fluorescent spectrometry
SD – standard deviation
SE – standard error of the mean

Several papers show that fluid zinc concentration for prostatitis is much lower than the normal level [6, 7, 14]. The estimates of zinc in seminal fluid contradict what has been mentioned earlier. It is known that prostatic fluid contributes greatly to ejaculate zinc content. A sharp decrease in zinc of prostatic fluid must result in lowering the element concentration in seminal fluid. However, no convincing examples of decreasing zinc content in seminal fluid have been found for prostatitis [3, 4]. The mean concentration of zinc in prostatic fluid obtained by us for chronic prostatitis is only 23% lower than the normal level. This decrease is not even statistically reliable.

The mean value of zinc fluid concentration for adenoma does not differ from the normal level. Anderson and Fair who analysed fluid zinc content in 25 patients suffering from benign prostatic hypertrophy have drawn the same conclusion [1]. The mean value we obtained closely approaches the mean zinc level given by Romics and Bach [21]. However, it is known that the zinc concentration for adenoma is significantly higher than that found in normal prostatic tissue [8, 11, 22]. Zinc concentration in the normal prostate averages 2–3 times less than that in normal fluid. It may be concluded that increased hyperplastic zinc concentration is probably connected with an increasing prostatic fluid volume, or more active zinc accumulation in the cellular fraction, or with influence of these two factors. Thus, Feustel et al. [9], for instance, discovered higher zinc concentrations in both the epithelial tissue fraction and stromal fraction in the benign hyperplastic prostate. Epithelial zinc concentration exceeded by more than 10 times the normal level and, taking into account the wet mass, it was equal to the concentration of zinc in secretion.

The sharp decrease of fluid zinc concentration we found in cancer patients contradicts the results obtained by Kavanagh et al. [14]. They analysed secretion taken from three patients suffering from prostatic carcinoma and found no difference from the normal level of zinc. Unfortunately, there was no information on disease grading in the paper. In our study, all the patients had T_3 or T_4 grade malignant tumours according to the Medical Clinical Classification of the TNM system. Anderson and Fair found an about 2-fold decrease of zinc concentration in the seminal fluid in patients with carcinoma, on average [1]. Of the patients they examined one had grade I, stage A, four had grade II, stages A and B, and three patients had grade IV, stage D disease. The analysis of the results available makes it possible to conclude that fluid zinc probably depends on a degree of prostatic involvement in the neoplastic process.

In addition to zinc, large amounts of the major electrolytes, such as K, Ca, and Mg, are also characteristic in prostatic fluid. These concentrations are much higher in prostatic fluid than in the other body fluids [15]. These electrolytes probably decrease greatly in cancer along with zinc. This fact may explain the lower fluid water content we found because the only known mechanism for biological water transport is implemented through the osmotic gradient.

It is assumed that a marked decrease in prostatic fluid zinc concentration for cancer can be used in establishing the diagnosis. On the one hand, XRF makes it possible to quickly and accurately obtain data about zinc content in a secretion specimen, the volume of which does not exceed one drop. Both factors make such a diagnostic approach very attractive. The results of our study (Fig. 1) permitted us to estimate the diagnostic value of zinc secretion content for the differential diagnosis of adenoma and malignant tumours of the prostate. A 100 μg/ml secretion limit was used for the selection. The characteristics of the diagnostic method were as follows:

$$\text{Sensitivity} = \{\text{correct positive test (CPT)}/ /[\text{CPT} + \text{false negative test (FNT)}]\} \times 100\% = 93 \pm 8\%.$$

$$\text{Specificity} = \{\text{correct negative test (CNT)}/ /[\text{CNT} + \text{false positive test (FPT)}]\} \times 100\% = 96 \pm 4\%.$$

$$\text{Accuracy} = [(\text{CPT} + \text{CNT})/(\text{CPT} + \text{FNT} + \text{CNT} + \text{FPT})] \times 100\% = 95 \pm 4\%.$$

Confidence intervals for the calculations, paying attention to the number of those examined, were taken from the corresponding tables of the paper [10]. If the zinc concentration is found to be not more than 100 μg/ml to analyse secretion specimens obtained by digital rectal prostatic massage, an accuracy of 95±4% is available to diagnose a neoplasm. Using the zinc secretion test makes it possible to find 93±8% of cancer cases (sensitivity).

However, the number of examined patients with prostatic cancer was rather small. Thus, the information about possible application of zinc fluid content in the differential diagnosis of adenoma and malignant tumours requires further careful control.

Acknowledgement

We express our gratitude to Mr. Peter Wagener, for correction of the English translation.

References

1. Anderson, R. U., Fair, W. R.: Physical and chemical determinations of prostatic secretion in benign hyperplasia, prostatitis, and adenocarcinoma. *Invest. Urol., 14,* 137 (1976).
2. Bertrand, G., Vladesco, R.: Intervention probable du zinc dans les phénomènes defécondation chez les animaux vertèbres. *C. R. Acad. Sci. (Paris), 173,* 176 (1921).
3. Boström, K., Andersson, L.: Creatine phosphokinase relative to acid phosphatase, lactate dehydrogenase, zinc and fructose in human semen with special reference to chronic prostatitis. *Scand. J. Urol. Nephrol., 5,* 123 (1971).
4. Colleen, S., Mardh, P. A., Schytz, A.: Magnesium and zinc in seminal fluid of healthy males and patients with non-acute prostatitis with and without gonorrhea. *Scand. J. Urol. Nephrol., 9,* 192 (1975).
5. Dunchik, V. N., Zherbin, E. A., Zaichick, V. Ye., Leonov, A. I., Sviridova, T. V.: Method for differential diagnostics of malignant and benign prostate tumors. *Discoveries, Inventions, Commercial Models, Trade Marks, 35,* 13 (1980).
6. Fair, W. R., Couch, J., Wehner, N.: Prostatic antibacterial factor. Identity and significance. *Urology, 7,* 169 (1976).
7. Fair, W. R., Cordonnier, J. J.: The pH of prostatic fluid: A reappraisal and therapeutic implications. *J. Urol., 120,* 695 (1978).
8. Feustel, A., Wennrich, R., Steiniger, D., Klauss, P.: Zinc and cadmium concentration in prostatic carcinomas of different histological grading in comparison to normal prostate tissue and adenofibromyomatosis (BPH). *Urol. Res., 10,* 301 (1982).
9. Feustel, A., Wennrich, R., Dittrich, H.: Zinc, cadmium and selenium concentrations in separated epithelium and stroma from prostatic tissues of different histology. *Urol. Res., 15,* 161 (1987).
10. Genes, V. S.: Simple Methods for Cybernetic Data Treatment of Diagnostic and Physiological Studies. Nauka, Moscow 1967.
11. Györkey, F., Min, K. W., Huff, J. A., Györkey, P.: Zinc and magnesium in human prostate gland: Normal, hyperplastic and neoplastic. *Cancer Res., 27,* 1348 (1967).
12. Habib, F. K., Mason, M. K., Smith, P. H., Stitch, S. R.: Cancer of the prostate: Early diagnostics by zinc and hormone analysis. *Br. J. Cancer, 39,* 700 (1979).
13. Homonnai, Z. T., Matzkin, H., Fainman, N., Paz, G., Kraicer, P. F.: The cation composition of the seminal plasma and prostatic fluid and its correlation to semen quality. *Fertil. Steril., 29,* 539 (1978).
14. Kavanagh, J. P., Darby, C., Costello, C. B.: The response of seven prostatic fluid components to prostatic disease. *Int. J. Androl., 5,* 487 (1982).
15. Kavanagh, J. P.: Zinc binding properties of human prostatic tissue, prostatic secretion and seminal fluid. *J. Reprod. Fertil., 68,* 359 (1983).
16. Kavanagh, J. P.: Sodium, potassium, calcium, magnesium, zinc, citrate and chloride content of human prostatic and seminal fluid. *J. Reprod. Fertil., 15,* 35 (1985).
17. Mackenzie, A. R., Hall, H., Whitmore, W. F. Jr.: Zinc content of expressed human prostatic fluid. *Nature, 193,* 72 (1962).
18. Marmar, J. L., Katz, S., Praiss, D. E., De Benedictis, T. J.: Values for zinc in whole semen fraction of split ejaculate and expressed prostatic fluid. *Urol., 16,* 478 (1980).
19. Mawson, C. A., Fischer, M. J.: The occurrence of zinc in the human prostate gland. *Can. J. Med. Sci., 30,* 336 (1952).
20. Parr, R.: Inter-comparison of minor and trace elements in IAEA animal muscle (H-4). Report No. 2. IAEA, Vienna 1980.
21. Romics, I., Bach, D.: Zn, Ca and Na levels in the prostatic secretion of patients with prostatic adenoma. *Int. Urol. Nephrol., 23,* 45 (1991).
22. Schrodt, G. R., Hall, T., Whitmore, W. R. Jr.: The concentration of zinc in diseased human prostate glands. *Cancer, 17,* 1556 (1964).