REVIEW ARTICLE

A Systematic Review of the Zinc Concentrations in the Prostate Fluid of Normal and Cancerous Gland

Vladimir Zaichick[1], Sofia Zaichick[1,2]

[1]Department of Radionuclide Diagnostics, Medical Radiological Research Centre, Koroleva St.-4, Obninsk 249036, Kaluga Region, Russia, [2]Department of Medicine, University of Illinois College of Medicine, Chicago, IL 60612, USA

ABSTRACT

Background: Prostate cancer (PCa) is the most commonly occurring neoplasm in males in many countries and the fourth most commonly occurring cancer overall. Various studies indicate some discrepancies regarding zinc (Zn) levels in prostatic fluid of normal and cancerous glands. **Materials and Methods:** The present systematic analysis included 25 studies on Zn levels in expressed prostatic fluid (EPF), all of which were published in the years from 1961 to 2018 and selected by searching the databases Scopus, PubMed, MEDLINE, ELSEVIER-EMBASE, Cochrane Library, and the Web of Science. The articles were analyzed, and "Median of Means" and "Range of Means" were used to examine heterogeneity of Zn concentrations in two groups of subjects – apparently healthy men "N" and patients with PCa "C." Moreover, using the ratios of prostatic fluid Zn in "C" group to prostatic fluid Zn in "N" group (Zn_C/Zn_N) obtained (or calculated by us) in the reviewed studies, "Median of Means" and "Range of Means" for these ratios were found. The objective analysis was performed on data from the 25 studies, with total 85 subjects in "C" group and more than 900 subjects in "N" group. **Results:** The range of means of Zn concentration reported in the literature for normal EPF varies widely from 47.1 mg/L to 825 mg/L with a median of means 501 mg/L. The range of means of Zn concentration for EPF of untreated cancerous prostate varies also widely from 34.7 mg/L to 722 mg/L, but median of means is lower – 65.4 mg/L. Thus, the obtained median of means for Zn concentration in normal human prostatic fluid is at least one order of magnitude higher than median of mean values of the element content in EPF of cancerous prostate. In other words, the analysis of 25 studies with discordant data regarding prostatic fluid concentration of Zn demonstrated that there is a significantly diminished concentration of Zn in EPF of PCa patients compared to controls. **Conclusions:** There is a significant relationship between lowered Zn concentrations in the prostatic fluid and PCa, but because of small sample size and high data heterogeneity, we recommend other primary studies.

Key words: Expressed prostatic fluid, prostate, prostate cancer, trace elements, zinc

INTRODUCTION

The prostate gland is subject to various disorders and of the prostate cancer (PCa) is one of the prostate's most important medical, scientific, and public health problems. Worldwide, PCa is the second most commonly diagnosed cancer and the fifth leading cause of cancer deaths in men.[1] PCa is especially prevalent in industrialized countries, including North America, Northern, and Western Europe, and Australia.[2] The American Cancer Society declares PCa, with a lifetime prevalence of one in six men, is the most common cancer in males and the second leading cause of cancer death.[3] PCa incidence is also steadily increasing in developing countries. For example, PCa is leading cancer in terms of incidence and mortality in men from Africa, Oceania, and the Caribbean.[1,2] PCa in China has also become a major public health concern.[4]

Address for correspondence:
Dr. Vladimir Zaichick, Department of Radionuclide Diagnostics, Medical Radiological Research Centre, 4, Koroleva St., Obninsk 249036, Kaluga Region, Russia. Phone/Fax: (48439) 60289/(495) 956 1440. E-mail: vzaichick@gmail.com

In our previous studies, the significant involvement of Zn, Ca, Mg, Rb, and some other trace elements (TEs) in the function of the prostate was found.[5-15] Moreover, it was demonstrated that the changes in Zn content and levels of Zn/TE ratio in the prostate tissue can be used as tumor markers.[16-25]

One of the main functions of the prostate gland is the production of prostatic fluid.[26] It contains a high concentration of Zn and elevated levels of Ca, Mg, Rb, and some other TEs, in comparison with levels in serum and other human body fluids. The first finding of remarkably high levels of Zn in human expressed prostatic fluid (EPF) was reported in the early 1960s.[27] After analyzing EPF expressed from the prostates of eight 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 suggested that the measurement of Zn levels in EPF may be useful as a marker of abnormal prostate secretary function.[28,29] This suggestion promoted more detailed studies of the Zn concentrations in the EPF of healthy subjects and those with different prostatic diseases, including PCa.[29,30]

For humans, Zn is an essential nutritional TE, especially in terms of proteins and nucleic acid metabolism. It is required for the catalytic activity of at least 300 enzymes and is involved in the human immune system, in tissue repair, and in DNA syntheses. There are a lot of data on the subject. For example, its role in cell immunity and as an antioxidant has recently been reviewed.[31-35] However, the exact role of Zn in normal and pathophysiology of the prostate is until now unknown.

The effects of TEs are related to concentration and recorded observations range from a deficiency state, to function as biologically essential components, to an unbalance when an excess of one element interferes with the function of another, to pharmacologically active concentrations, and finally to toxic and even life-threatening concentrations.[36,37] In this context, the role in neoplastic growth and malignancy has been associated with elevated Zn contents in body fluids and tissues for a long time.[34,36-40]

Several studies have reported the Zn content in EPF of normal and cancerous gland.[27-30,41-59] However, further investigation has been considered necessary to provide a clearer hypothesis about the role of Zn in PCa. Moreover, some studies have reported changed prostatic fluid Zn levels as an indicator or biomarker of PCa.[29,30,54,55] However, the findings of various studies indicate some discrepancies. One researcher has demonstrated that prostatic fluid level of Zn increases in PCa patients compared to controls,[27] while others have found the opposite effect.[29,30,54,55,59]

The present study addresses the significance of prostatic fluid Zn levels in PCa. Therefore, we systematically reviewed the available literature and performed a statistical analysis to evaluate the effect of malignant transformation on prostatic fluid Zn concentration, which may shed valuable insight into the diagnosis of PCa.

MATERIALS AND METHODS

Data sources and search strategy

Aiming at finding the most relevant articles for this review, a thorough comprehensive web search was conducted from Scopus, PubMed, MEDLINE, ELSEVIER-EMBASE, Cochrane Library, and the Web of Science databases between 1961 and November 2019, using the keywords: PCa, TEs, Zn concentration, EPF, and their combination. For example, the search terms for Zn concentration were: "Zn concentration," "Zn content," "Zn level," "prostatic fluid Zn," and "Zn of EPF," while those for PCa were: "PCa," "prostate malignancy," and "prostate neoplasia." The language was not restricted. The titles from the search results were evaluated closely and determined to be acceptable for potential inclusion criteria. Furthermore, references from the selected articles were examined as further search tools. Relevant studies noted in the reference lists of each selected article were also evaluated for inclusion.

Eligibility criteria

Inclusion criteria

Studies were included if patients met the diagnostic criteria of PCa. The controls were healthy human males with no history or evidence of andrologia or urologic disease. Zinc (Zn) was detected in samples of EPF.

Exclusion criteria

Studies were excluded from the study if they were case reports. Studies involving patients with PCa that was undergoing Zn supplementation therapy were also excluded from the study.

Data extraction

A standard extraction of data was applied, and the following available variables were extracted from each paper for two groups of subjects with normal "N" and cancerous "C" prostate: Method of Zn determination, number and age of healthy person and patients, samples preparing, means and medians of Zn concentrations, standard deviations of means, range of Zn concentrations, and statistical difference of means. Abstracts and full articles were reviewed independently by two of the authors, and if the results were different, papers were checked jointly until the differences were resolved.

Statistical analysis

Studies were combined based on means of Zn concentrations in EPF. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine the heterogeneity of

Zn concentrations in two groups of subjects – "N" and "C." Moreover, using the ratios of prostatic fluid Zn in "C" group to prostatic fluid Zn in "N" group (Zn_C/Zn_N) obtained (or calculated by us) in the reviewed studies, "Median of Means" and "Range of Means" for these ratios were also found. The objective analysis was performed on data from the 25 studies, with a total of 85 subjects in "C" group and more than 900 subjects in "N" group. In addition, two subgroups of data from group "N" were used to evaluate the difference between results obtained by destructive and non-destructive analytical methods.

RESULTS

A total of 1885 unduplicated studies were identified. Among them, 25 studies were ultimately selected according to eligibility criteria, including 25 studies that investigated Zn concentrations in EPF of normal prostate [Table 1] and seven studies that investigated Zn concentrations in EPF of both normal and cancerous prostate [Table 2]. After discussion, all reviewers were in agreement to include all 25 papers.

Table 1: Reference data of Zn concentration in normal human prostatic fluid (group "N")

Reference	Method	*n*	Age, years M (Range)	Samples preparing	Zn, mg/L	
					M±SD (Med)	Range
Birnbaum *et al.* 1961[41]	XRF	-	-	Intact	490	-
Mackenzie *et al.* 1962[27]	XRF	8	37 (25–55)	Intact	490±130	265–666
Burgos, 1974[42]	-	-	-	-	47.1	-
Marmar *et al.* 1975[43]	AAS	33	-	AD	451±215	-
Anderson and Fair, 1976[44]	AAS	15	50 (30–74)	AD	352±190	-
Fair *et al.* 1976[45]	AAS	49	52 (24–76)	AD	455±208	150–1000
Paz *et al.* 1977[46]	AAS	53	-	AD	299±202	-
Fair and Cordonnier 1978[47]	AAS	63	52 (24–76)	AD	455±208	-
Homonnai *et al.* 1978[48]	AAS	12	-	AD	335±45	-
Marmar *et al.* 1980[28]	AAS	33	-	AD	451±215	-
Zaichick *et al.* 1981[29]	EDXRF	15	-	Intact	580±183	-
Zaneveld and Tauber 1981[49]	-	-	-	-	50.3	-
Kavanagh and Darby 1982[50]	AAS	35	49.2	AD	580	-
Kavanagh 1983[51]	AAS	152	-	AD	595±222	52–1308
Zaichick *et al.* 1996[30]	EDXRF	22	49 (22–75)	Intact	590±210	291–1118
Mo *et al.* 2000[52]	ICPAES	25	57.4±6.8	AD	305	243–379
Caietal 2002*[53]	AAS	22	-	AD	220±85	-
Gomes *et al.* 2007[54]	AAS	10	44 (40–62)	AD	519±374	131–1242
Costello and Franklin 2009[55]	EDXRF	24	-	Intact	588	-
Zhuang *et al.* 2009*[53]	AAS	20	-	AD	802±39	-
He *et al.* 2013*[53]	AAS	40	-	AD	825±71	-
Zaichick and Zaichick 2018[56]	EDXRF	41	18–82	Intact	573±202 (552)	253–948
		13	28 (18–40)	Intact	501±47	-
		38	59 (41–82)	Intact	598±34	-
Zaichick and Zaichick 2018[57]	EDXRF	42	31–75	Intact	559±204 (549)	253–948
Zaichick and Zaichick 2019[58]	EDXRF	38	41–82	Intact	598±207 (560)	253–948
Zaichick and Zaichick 2019[59]	EDXRF	38	41–82	Intact	598±207 (560)	253–948
Median of means, mg/L				501		
Range of means (M_{min}–M_{max}), mg/L				47.1–825		
Ratio M_{max}/M_{min}				(825/47.1)=17.5		

*Data of Chinese researches taken from the review Cui *et al.* 2015. M: Arithmetic mean, SD: Standard deviation of mean, Med: Median, XRF: X-ray fluorescence, AAS: Atomic absorption spectrophotometry, EDXRF: Energy dispersive X-ray fluorescence, ICPAES: Inductively coupled plasma atomic emission spectrometry, AD: Acid digestion, Zn: Zinc

Table 2: Reference data of Zn concentration in human prostatic fluid of normal (N) and cancerous (C) gland

Reference	Method	*n*	Age, years M (Range)	Group "N" or "C"	Zn, mg/L M±SD	Zn_c/Zn_n
Anderson and Fair, 1976[44]	AAS	15	50 (30–74)	N	352±190	0.634
		8	64 (51–76)	C	223±297	
Zaichick *et al.* 1981[29]	EDXRF	15	-	N	580±183	0.069
		13	-	C	40.2±54.1*	
Kavanagh and Darby 1982[50]	AAS	35	49.2	N	580	1.24
		3	71.8	C	722	
Zaichick *et al.* 1996[30]	EDXRF	22	49 (22–75)	N	590±210	0.059
		13	67 (47–81)	C	34.7±34.6*	
Gomes *et al.* 2007[54]	AAS	10	44 (40–62)	N	519±374	0.129
		9	66 (47–86)	C	67.2±50.9*	
Costello and Franklin 2009[55]	EDXRF	24	-	N	588	0.111
		15	-	C	65.4*	
Zaichick and Zaichick 2019[59]	EDXRF	38	41–82	N	598±207	0.104
		24	47–77	C	62±98*	
Group "N"	Median of means, mg/L				580	
	Range of Means (M_{min}–M_{max}), mg/L				352–598	
Group "C"	Median of means, mg/L				65.4	
	Range of Means (M_{min}–M_{max}), mg/L				34.7–722	
Ratio Zn_C/Zn_N	Median of means				0.111	
	Range of Means (M_{min}–M_{max})				0.059–1.24	

*Statistically significant differences between group "N" and "C." M: Arithmetic mean, SD: Standard deviation of mean, AAS: Atomic absorption spectrophotometry, EDXRF: Energy dispersive X-ray fluorescence, Zn: Zinc

Tables 1 and 2 summarize general data from the 25 studies. The retrieved studies involved 85 patients with PCa and more than 900 normal controls. The ages of subjects in "N" group were available for 14 studies and ranged from 18 to 82 years. The ages of subjects in "C" group were available for five studies and ranged from 41 to 86 years. The mean ages of subjects in the control and patient groups were available for ten and three studies, respectively. The information about analytical method was available for 23 studies. Fourteen studies determined Zn concentration by the destructive analytical methods: Thirteen using atomic absorption spectrophotometry (AAS) and one using inductively coupled plasma-atomic emission spectrometry (ICP-AES). Nine studies detected Zn concentration in EPF by the nondestructive analytical methods, such as XRF (X-ray fluorescence analysis, two studies) and EDXRF (energy dispersive X-ray fluorescence analysis, seven studies). Tables 3 and 4 present data of Zn concentration in EPF of normal prostates obtained by the destructive and nondestructive analytical methods, respectively.

DISCUSSION

Samples of EPF are much more available for study than prostate tissue and can be obtained without damaging the prostate gland. Information about Zn concentrations in prostatic fluid in different prostatic diseases is of obvious interest, not only to more profoundly understand the etiology and pathogenesis of prostatic diseases but also for their diagnosis, particularly for PCa diagnostics.[29,30,54,55,59] Thus, it dictates a need in reliable values for the Zn concentrations in the EPF of apparently healthy subjects ranging from young adult males to elderly persons, as well as in the EPF of patients with PCa.

The range of means of Zn concentration reported in the literature for normal EPF varies widely from 47.1 mg/L[42] to 825 mg/L[53] with a median of means 501 mg/L [Table 1].

In the present study, seven articles studied the effect of malignant transformation on the Zn concentration of EPF [Table 2]. Six of the seven articles studied the impact of malignancy on Zn concentration in EPF reported that there was a decrease of Zn level. In five of the six articles were found that they dramatical decrease of Zn level was statistically significant[29,30,54,55,59] and only one study showed the relatively small and non-statistical significant decrease.[44] In a study with very short sample size of cancer patients (n = 3) conducted by Kavanagh and Darby,[50] it was observed that mean of Zn concentration in EPF was

Table 3: Reference data of Zn concentration in normal prostatic fluid investigated by destructive AAS and ICP-AES methods

References	Method	*n*	Age, years M (Range)	Zn, mg/L M±SD
Marmar *et al*. 1975[43]	AAS	33	-	451±215
Anderson and Fair, 1976[44]	AAS	15	50 (30–74)	352±190
Fair *et al*. 1976[45]	AAS	49	52 (24–76)	455±208
Paz *et al*. 1977[46]	AAS	53	-	299±202
Fair and Cordonnier 1978[47]	AAS	63	52 (24–76)	455±208
Homonnai *et al*. 1978[48]	AAS	12	-	335±45
Marmar *et al*. 1980[28]	AAS	33	-	451±215
Kavanagh and Darby 1982[50]	AAS	35	49.2	580
Kavanagh 1983[51]	AAS	152	-	595±222
Mo *et al*. 2000[52]	ICP-AES	25	57.4±6.8	305
Caietal 2002*[53]	AAS	22	-	220±85
Gomes *et al*. 2007[54]	AAS	10	44 (40–62)	519±374
Zhuang *et al*. 2009*[53]	AAS	20	-	802±39
He *et al*. 2013*[53]	AAS	40	-	825±71
Median of means, mg/L	453			
Range of means (M_{min}–M_{max}), mg/L	220–825			
Ratio M_{max}/M_{min}	(825/220)=3.75			

*Data of Chinese researches taken from the review Cui *et al*. 2015. M: Arithmetic mean, SD: Standard deviation of mean, AAS: Atomic absorption spectrophotometry, ICPAES: Inductively coupled plasma atomic emission spectrometry, Zn: Zinc

Table 4: Reference data of Zn concentration in normal prostatic fluid investigated by nondestructive XRF and EDXRF methods

Reference	Method	*n*	Age, years M (Range)	Zn, mg/L M±SD
Birnbaum *et al*. 1961[41]	XRF	-	-	490
Mackenzie *et al*. 1962[27]	XRF	8	37 (25–55)	490±130
Zaichick *et al*. 1981[29]	EDXRF	15	-	580±183
Zaichick *et al*. 1996[30]	EDXRF	22	49 (22–75)	590±210
Costello and Franklin 2009[55]	EDXRF	24	-	588
Zaichick and Zaichick 2018[56]	EDXRF	41	18–82	573±202
		13	28 (18–40)	501±47
		38	59 (41–82)	598±34
Zaichick and Zaichick 2018[57]	EDXRF	42	31–75	559±204
Zaichick and Zaichick 2019[58]	EDXRF	38	41–82	598±207
Zaichick and Zaichick 2019[59]	EDXRF	38	41–82	598±207
Median of means, mg/L			580	
Range of means (M_{min}–M_{max}), mg/L			490–598	
Ratio M_{max}/M_{min}			(598/490)=1.22	

M: Arithmetic mean, SD: Standard deviation of mean, XRF: X-ray fluorescence, EDXRF: Energy dispersive X-ray fluorescence, Zn: Zinc

higher than in control group, but the difference between cancer patients and normal controls was not statistically significant. In all our studies, the Zn concentrations in EPF from cancer patients were significantly lower than normal controls.[29,30,59]

The range of means of Zn concentration reported in these seven articles for normal EPF varies relatively slightly from 352 mg/L[44] to 598 mg/L,[59] with median of means 580 mg/L [Table 2]. However, the range of means of Zn concentration for EPF of untreated cancerous prostate varies widely

from 34.7 mg/L[30] to 722 mg/L,[50] with median of means 65.4 mg/L [Table 2]. Thus, the obtained median of means for Zn concentration in normal human prostatic fluids at least one order of magnitude higher than median of mean values of the element content in EPF of cancerous prostate. In other words, the analysis of seven studies with discordant data regarding prostatic fluid concentration of Zn demonstrated that there is a significantly diminished concentration of Zn in EPF of PCa patients compared to controls. It is, therefore, reasonable to assume that Zn level in EPF can be very useful as PCa biomarker.

As indicated above, the range of means of Zn concentration reported in the literature for normal EPF and for EPF of untreated cancerous prostate varies widely. 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. However, published data allowed us to estimate the effect of age on Zn concentration in EPF of the normal prostate. In one study a significant increase in Zn concentration with increasing age was shown by Pearson's coefficient of correlation between age and Zn concentration in EPF.[56] According this study, Zn concentration in EPF of apparently healthy men aged 41–82 years was about 20% higher than in age from 18 to 40 years. However, this finding does not agree with other published data. For example, in the first quantitative XRF analysis of Zn concentration in EPF of eight apparently healthy men aged 25–55 years no significant variation with age was recognized, in spite of no statistical treatment of results was done in this investigation.[27] Fair and Cordonnier[47] did not find any changes in metal level with age using AAS for Zn measurement in EPF specimens obtained from 63 normal male subjects in age from 24 to 76 years. The conclusion was followed from the level of differences between the mean Zn results for three age groups evaluated by parametric Student's *t*-test. In addition, Zn, concentration in prostatic fluid showed no age relationship in the study of Kavanagh and Darby[50] when 35 specimens obtained from normal male subjects in age from 15 to 85 years were measured by AAS and the Pearson correlation between age and Zn concentration was used. It is, therefore, reasonable to assume that Zn level in EPF does not change with age or, at least, slightly increase in age above 40 years.

Another and, in our opinion, leading cause of inter-observer variability was insufficient quality control of results in these studies. In many reported papers, such destructive analytical methods as AAS and ICP-AES were used. These methods need in sample acid digestion under high temperatures. There is evidence that by the use of this treatment some quantities of TEs, including Zn, is lost.[60-62] On the other hand, TEs of chemicals used for acid digestion can contaminate the EPF samples. Such method as XRF and, particularly, EDXRF is a fully instrumental and non-destructive analytical tool because a drop of EPF is investigated without requiring any sample pre-treatment or its consumption.[63]

In the present study, in 14 articles, Zn concentration in EPF samples was determined by the destructive analytical methods (13 articles – AAS and one articles – ICP-AES), and in nine articles non-destructive analytical methods were used for this purpose (two articles – XRF and seven articles – EDXRF). Thus, published data allowed us to estimate the effect of acid digestion at the results of Zn determination in EPF on normal prostates [Tables 3 and 4]. In articles with destructive analytical methods, the range of means for Zn concentration in EPF of normal prostates varied from 220 mg/L to 825 mg/L (ratio Mmax/Mmin = 3.75), with median of means 453 mg/L [Table 3]. The articles with non-destructive analytical methods have a rather narrow range of means for Zn concentration in EPF of normal prostates from 490 mg/L to 598 mg/L (ratio Mmax/Mmin = 1.22), with median of means 580 mg/L. Thus, median of means for Zn concentration in EPF of normal prostates obtained by destructive analytical methods is 22% lower than that obtained by nondestructive methods. It is, therefore, reasonable to conclude that the choice of analytical method and quality control of results are very important factors for using the Zn concentration in EPF as PCa biomarker.

There is some limitation in our study, which need to be taken into consideration when interpreting the results of this review. The sample size of each study was relatively small, and a total of 85 PCa patients and about 900 normal controls were investigated from all 25 studies. As such, it is hard to make definitive conclusions about the clinical value of the Zn concentration in EPF as PCa biomarker.

CONCLUSIONS

The present study is a comprehensive study regarding the determination of Zn concentration in EPF as a biomarker for PCa development. The study has demonstrated that Zn concentration levels are drastically decreased in EPF samples of patients with PCa. The present study also demonstrates that EPF samples could be considered reliable sources for Zn biomarker analysis. Because of high heterogeneity, we recommend other primary studies.

AUTHORS' CONTRIBUTIONS

SZ analyzed and interpreted the data regarding the normal and cancerous prostate. VZ analyzed and interpreted the data regarding the analytical methods and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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