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Research Article

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

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Abstract

The prostate gland is subject to various disorders. The etiology and pathogenesis of these diseases are not well understood. Moreover, despite technological advancements, the differential diagnostics of prostate disorders has become progressively more complex and controversial. It was suggested that the measurement of Zn levels in expressed prostatic fluid (EPF) may be useful as a biomarker. This suggestion promoted more detailed studies of the Zn concentrations in the EPF of healthy subjects. The present study evaluated by systematic analysis the published data for Zn concentration analyzed in EPF of normal gland. It included 25 studies, 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 EPF of apparently healthy men. The objective analysis was performed on data from the 25 studies, with more than 900 subjects. It was found that 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 median of means 501 mg/L. Finally, because of small sample size and high data heterogeneity, we recommend other primary studies.

Keywords: Prostate; Prostatic Fluid; Biomarkers; Trace Elements; Zinc

Abbreviations

PCa: Prostate Cancer; PSA: Prostate-Specific Antigen; TE: Trace Element; EPF: Expressed Prostatic Fluid; AAS: Atomic Absorption Spectrophotometry; ICPAES: Inductively Coupled Plasma Atomic Emission Spectrometry; XRF: X-Ray Fluorescence Analysis; EDXRF: Energy Dispersive X-Ray Fluorescent Microanalysis.

Introduction

The prostate gland is subject to various disorders and of them chronic prostatitis, benign prostatic hyperplasia, and prostate cancer (PCa) are the extremely common diseases of ageing men [1-3]. The etiology and pathogenesis of these diseases are not well understood. Moreover, despite technological advancements, the differential diagnostics of prostate disorders has become progressively more complex and controversial. This is particularly concerned with prostate cancer where the limitations and potential harms associated with the use of prostate-specific antigen (PSA) as a diagnostic marker. The situation stimulates significant investigation of numerous novel biomarkers that demonstrate varying capacities to detect prostate cancer and can decrease unnecessary biopsies [4].

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 of Zn content and levels of Zn/TE ratio in the prostate tissue can be used as biomarkers [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 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 suggested that the measurement of Zn levels in EPF may be useful as a marker of abnormal prostate secretory function [28,29]. This suggestion promoted more detailed studies of the Zn concentrations in the EPF of healthy subjects and in those with different prostatic diseases, including PCa [29,30].

For humans, Zn is an essential nutritional TE, especially in terms of proteins and nucleic acids 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 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 affected gland [29,30,41-61]. However, further investigation has been considered necessary to provide clearer hypothesis about the role of Zn in etiology and pathogenesis of prostate disorders, because the findings of various studies indicate some discrepancies.

The present study addresses the significance of prostatic fluid Zn levels as biomarker. Therefore, we systematically reviewed the available literature and performed a statistical analysis of Zn concentration in EPF of normal gland, which may shed valuable insight into the etiology and diagnosis of prostate disorders.

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, as well as from the personal archive Prof., Dr. Zaichick V. collected between 1961 to November 2019, using the key words: trace elements, Zn concentration, expressed prostatic fluid, and their combination. For example, the search terms for Zn concentration were: 'Zn concentration', 'Zn content', 'Zn level', 'prostatic fluid Zn' and "Zn of expressed prostatic fluid". The language was not restricted. The titles from the search results were evaluated closely and determined to be acceptable for potential inclusion criteria. Also, 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 the control groups were healthy human males with no history or evidence of andrologia or urologic disease and Zn was detected in samples of EPF.

Exclusion criteria

Studies were excluded if they were case reports. Studies involving subjects that were using Zn supplementation were also excluded.

Data extraction

A standard extraction of data was applied, and the following available variables were extracted from each paper: method of Zn determination, number and age of health persons, samples preparing, mean and median of Zn concentrations, standard deviations of mean, and range of Zn concentrations. 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 heterogeneity of Zn concentrations. The objective analysis was performed on data from the 25 studies, with more than 900 healthy subjects. In addition, two subgroups of data were used to evaluate the difference between results obtained for Zn concentrations in EPF by destructive and non-destructive analytical methods.

Results and 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 prostate cancer diagnostics [29,30,56,57,61]. 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.

A total of 1885 unduplicated studies were identified. Among them 25 studies were ultimately selected according to eligibility criteria, that investigated Zn concentrations in EPF of normal prostate (Table 1). After discussion, all reviewers were in agreement to include all 25 papers.

Table 1 summarizes general data from the 25 studies. The retrieved studies involved more than 900 apparently healthy subjects. The ages of subjects were available for 14 studies and ranged from 18–82 years. The information about analytical method was available for 23 studies. Fourteen studies determined Zn concentration by the destructive analytical methods: thirteen using AAS (atomic absorption spectrophotometry) and one using ICPAES (inductively coupled plasma atomic emission spectrometry). Nine studies detected Zn concentration in EPF by the nondestructive analytical methods, such as X-ray fluorescence analysis (XRF, 2 studies) and energy dispersive X-ray fluorescence analysis (EDXRF, 7 studies). Tables 2 and 3 present data of Zn concentration in EPF of normal prostates obtained by the destructive and nondestructive analytical methods, respectively.

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 [42]	XRF	8	37(25-55)	Intact	490 ± 130	265-666
Burgos, 1974 [43]	-	-	-	-	47.1	-
Marmar., *et al*. 1975 [44]	AAS	33	-	AD	451 ± 215	-
Anderson&Fair, 1976 [45]	AAS	15	50(30-74)	AD	352 ± 190	-
Fair., *et al*. 1976 [46]	AAS	49	52(24-76)	AD	455 ± 208	150-1000
Paz., *et al*. 1977 [47]	AAS	53	-	AD	299 ± 202	-
Fair&Cordonnier 1978 [48]	AAS	63	52(24-76)	AD	455 ± 208	-
Homonnai., *et al*. 1978 [49]	AAS	12	-	AD	335 ± 45	-
Marmar., *et al*. 1980 [50]	AAS	33	-	AD	451 ± 215	-
Zaichick., *et al*. 1981 [29]	EDXRF	15	-	Intact	580 ± 183	-
Zaneveld&Tauber 1981 [51]	-	-	-	-	50.3	-
Kavanagh., *et al*. 1982 [52]	AAS	35	49.2	AD	580	-
Kavanagh 1983 [53]	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 [54]	ICPAES	25	57.4 ± 6.8	AD	305	243-379
Cai., *et al.* 2002* [55]	AAS	22	-	AD	220 ± 85	-
Gómez., *et al*. 2007 [56]	AAS	10	44(40-62)	AD	519 ± 374	131-1242
Costello&Franklin 2009 [57]	EDXRF	24	-	Intact	588	-
Zhuang., *et al.* 2009* [55]	AAS	20	-	AD	802 ± 39	-
He., *et al.* 2013*[55]	AAS	40	-	AD	825 ± 71	-
Zaichick&Zaichick 2018 [58]	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 [59]	EDXRF	42	31-75	Intact	559 ± 204 (549)	253-948
Zaichick and Zaichick 2018 [60]	EDXRF	38	41-82	Intact	598 ± 207 (560)	253-948
Zaichick and Zaichick 2018 [61]	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					

Table 1: Reference data of Zn concentration in normal human prostatic fluid.

*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

The range of means of Zn concentration reported in the literature for normal EPF varies widely from 47.1 mg/L [43] to 825 mg/L [55] with median of means 501 mg/L (Table 1).

As indicated above, the range of means of Zn concentration reported in the literature for normal EPF 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 normal prostate. In one study a significant increase in Zn concentration with increasing of age was shown by the Pearson's coefficient of correlation between age and Zn concentration in EPF [58]. 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. But this finding does not agree with other published data. For example, in the first quantitative XRF analysis of Zn concentration in EPF of 8 apparently healthy men aged 25-55 years no significant variation with age was recognized, in spite of no any statistical treatment of results was done in this investigation [42]. Fair and Cordonnier [48] did not find any changes in metal level with age using AAS for Zn measurement in

Reference	Method	n	Age, years M (Range)	Zn, mg/L M ± SD
Marmar., *et al*. 1975 [44]	AAS	33	-	451 ± 215
Anderson&Fair, 1976 [45]	AAS	15	50(30-74)	352 ± 190
Fair., *et al*. 1976 [46]	AAS	49	52(24-76)	455 ± 208
Paz., *et al*. 1977 [47]	AAS	53	-	299 ± 202
Fair and Cordonnier 1978 [48]	AAS	63	52(24-76)	455 ± 208
Homonnai., *et al*. 1978 [49]	AAS	12	-	335 ± 45
Marmar., *et al*. 1980 [50]	AAS	33	-	451 ± 215
Kavanagh., *et al*. 1982 [52]	AAS	35	49.2	580
Kavanagh 1983 [53]	AAS	152	-	595 ± 222
Mo., *et al*. 2000 [54]	ICP-AES	25	57.4 ± 6.8	305
Cai., *et al*. 2002* [55]	AAS	22	-	220 ± 85
Gómez., *et al*. 2007 [56]	AAS	10	44(40-62)	519 ± 374
Zhuang., *et al*. 2009* [55]	AAS	20	-	802 ± 39
He., *et al*. 2013* [55]	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			

Table 2: Reference data of Zn concentration in normal prostatic fluid investigated by destructive AAS and ICP-AES methods.

*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.

Reference	Method	n	Age, years M (Range)	Zn, mg/L M ± SD
Birnbaum., *et al*. 1961 [41]	XRF	-	-	490
Mackenzie., *et al*. 1962 [42]	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 [57]	EDXRF	24	-	588
Zaichick and Zaichick 2018 [58]	EDXRF	41	18-82	573 ± 202
		13	28(18-40)	501 ± 47
		38	59(41-82)	598 ± 34
Zaichick and Zaichick 2018 [59]	EDXRF	42	31-75	559 ± 204
Zaichick and Zaichick 2018 [60]	EDXRF	38	41-82	598 ± 207
Zaichick and Zaichick 2018 [61]	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			

Table 3: Reference data of Zn concentration in normal prostatic fluid investigated by nondestructive XRF and EDXRF methods.

M: Arithmetic Mean; SD: Standard Deviation of Mean; XRF: X-Ray Fluorescence; EDXRF: Energy Dispersive X-Ray Fluorescence.

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. Additionally, Zn, concentration in prostatic fluid showed no age relationship in the study of Kavanagh., *et al*. [52] 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 do 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 temperature. There is evidence that by use of this treatment some quantities of TEs, including Zn, are lost [62-64]. On the other hand, TEs of chemicals used for acid digestion can contaminate the EPF samples. Thus, when using destructive analytical methods it is necessary to control for the losses of trace elements, for complete acid digestion of the sample, and for the

contaminations by trace elements during sample decomposition, which needs adding some chemicals. It is possible to avoid these not easy procedures using non-destructive methods. Such method as XRF and, particularly, EDXRF is a fully instrumental and nondestructive analytical tool because a drop of EPF is investigated without requiring any sample pretreatment or its consumption [65].

In present study, in 14 articles Zn concentration in EPF samples was determined by the destructive analytical methods (13 articles - AAS and 1 articles – ICP-AES) and in 9 articles nondestructive analytical methods were used for this purpose (2 articles – XRF and 7 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 2 and 3). 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 nondestructive analytical methods have the 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 biomarker.

The obtained median of means for Zn concentrations in normal human prostatic fluid was two orders of magnitude higher than mean values of the element content in blood serum and breast milk, and three orders of magnitude higher than in urine and mixed saliva (Table 4). So, it was confirmed that the human prostatic secretion is a target fluid of human body for Zn.

Human body fluid	Zn concentration, mg/L	Reference	Ratio Zn_{EPF}/Zn_{Fluid}
Expressed prostatic fluid	580	This review	1.0
Blood serum	0.95	[66]	611
Urine	0.25	[66]	2320
Mixed saliva	0.469±0.028	[67]	1237
Milk	1.5	[66]	387

Table 4: The differences between the mean of Zn concentration in the human expressed prostatic fluid of normal gland and in blood serum, urine, saliva, and milk of Reference Man (mg/L).

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 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 biomarker.

Conclusions

The present study is a comprehensive study regarding the determination of Zn concentration in EPF as a biomarker for the diagnostics of prostate disorders. The study has demonstrated that Zn concentration in EPF is two orders of magnitude higher than mean values of the element content in blood serum and breast milk, and three orders of magnitude higher than in urine and mixed saliva. Level of Zn in EPF does not depend from age. There is difference between results obtained by destructive and nondestructive analytical methods. Because of high heterogeneity, we recommend other primary studies.

Conflict of Interest

The authors declare that there no conflict of interest.

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