

A systematic review of the main electrolytes concentrations in the prostate fluid of normal gland

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 main electrolytes levels in expressed prostatic fluid (EPF) may be useful as a biomarker. This suggestion promoted more detailed studies of the Ca, Cl, K, Mg, and Na concentrations in the EPF of healthy subjects. The present systematic analysis included 1885 studies, all of which were published in the years from 1942 to 2019 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 Ca, Cl, K, Mg, and Na concentrations in EPF of apparently healthy men. The objective analysis was performed on data from the 6 studies, with more than 62 subjects. It was found that the median of means for Ca, Cl, K, Mg, and Na concentrations in prostatic fluid of apparently healthy men were 1201, 1350, 1880, 486, and 3517 mg/L, respectively. Because of small sample size and high data heterogeneity, we recommend other primary studies.

Keywords: prostate, prostatic fluid, biomarkers, main electrolytes, calcium, chlorine, potassium, magnesium, sodium

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Abbreviations: PSA, prostate-specific antigen; Ca, calcium; Cl, chlorine; K, potassium; Mg, magnesium; Na, sodium; ME, main electrolyte; TE, trace element; EPF, expressed prostatic fluid; Chem, traditional chemical analytical method; FES, flame emission spectrophotometry; AAS, atomic absorption spectrophotometry; 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 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 zinc (Zn), calcium (Ca), magnesium (Mg), rubidium (Rb) and some other main electrolytes (MEs) and trace elements (TEs) in the normal physiology of the prostate was found.⁵⁻³⁰ It was also found a great deformation of chemical element concentrations in affected prostate and was demonstrated that the changes of some MEs and TE content, as well as levels of some ME/TE ratios in the prostate tissue can be used as the biomarkers of prostate diseases,³¹⁻⁴¹ and global environmental contamination.⁴² Moreover, it was shown that levels of some MEs and TE in prostate tissue play a very important role in carcinogenesis of the gland.⁴³⁻⁴⁵

One of the main functions of the prostate gland is the production of prostatic fluid.⁴⁶ It contains a high concentration of Ca, Mg, Rb, Zn and some other TEs, in comparison with levels in blood 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.⁴⁷ 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.^{48,49} This suggestion promoted more detailed studies of the MEs and TE concentrations in the EPF of healthy subjects and in those with different prostatic diseases, including PCa.⁴⁹⁻⁶⁹ MEs, such as Ca, chlorine (Cl), potassium (K), Mg, and sodium (Na) are vital for the normal functioning of the human body,⁷⁰ there are a lot of data on the subject. However, the exact role of MEs in normal and pathophysiology of the prostate gland, specifically the prostatic fluid, is until now unknown.

Several studies have reported the MEs content in EPF of normal and affected gland.⁷¹⁻⁷⁸ However, further investigation has been considered necessary to provide clearer hypothesis about the role of MEs 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 Ca, Cl, K, Mg, and Na levels as biomarker. Therefore, we systematically reviewed the available literature and performed a statistical analysis of Ca, Cl, K, Mg, and Na concentration in EPF of normal gland, which may shed valuable insight into the etiology and diagnosis of prostate disorders.

Material 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 1942 to November 2019, using the key words: main electrolytes, calcium concentration, chlorine concentration, potassium concentration, magnesium concentration, sodium concentration, expressed prostatic fluid, and their combination. For example, the search terms for MEs concentration were: 'calcium concentration', 'Ca concentration', 'calcium content', 'Ca content', 'calcium level', 'Ca level', 'prostatic fluid calcium', 'prostatic fluid Ca', 'calcium of expressed prostatic fluid', and 'Ca 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

Studies were included if the control groups were healthy human males with no history or evidence of andrologia or urologic disease and Ca, Cl, K, Mg, or Na were detected in samples of EPF.

Studies were excluded if they were case reports or reviews. Studies involving subjects that were using Ca, K, and Mg 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 MEs determination, number and age of health persons, samples preparing, mean and median of Ca, Cl, K, Mg, and Na concentrations, standard deviations of mean, and range of MEs concentrations.

Statistical analysis

Studies were combined based on means of Ca, Cl, K, Mg, and Na concentrations in EPF. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of MEs concentrations. The objective analysis was performed on data from the 6 studies, with more than 62 healthy subjects.

Results

A total of 1885 unduplicated studies were identified. Among them 6 studies were ultimately selected according to eligibility criteria, that investigated Ca, Cl, K, Mg, and Na concentrations in EPF of normal prostate (Tables 1–5), respectively.

Table 1 summarizes general data from the 6 studies on Ca concentrations in EPF samples. The retrieved studies involved more than 49 apparently healthy subjects. The ages of subjects were not presented. The information about analytical method was available for 3 studies. One study determined Ca concentration by the traditional chemical analytical method,⁷¹ and two using atomic absorption spectrophotometry (AAS).^{73,75}

Table 2 summarizes general data from the 5 studies on Cl concentrations in EPF samples. The retrieved studies involved more than 46 apparently healthy subjects. The ages of subjects were not presented. The information about analytical method was available for 2 studies. Both studies determined Cl concentration by the traditional chemical analytical method.^{71,75}

Table 3 summarizes general data from the 5 studies on K concentrations in EPF samples. The retrieved studies involved more than 40 apparently healthy subjects. The ages of subjects were not presented. The information about analytical method was available for 2 studies. One study determined K concentration by the traditional chemical analytical method,⁷¹ and other one using flame emission spectrophotometry (FES).⁷⁵

Table 4 summarizes general data from the 4 studies on Mg concentrations in EPF samples. The retrieved studies involved more than 46 apparently healthy subjects. The ages of subjects were not presented. The information about analytical method was available for 2 studies. Both studies determined Mg concentration using atomic absorption spectrophotometry (AAS).^{73,75}

Table 5 summarizes general data from the 5 studies on Na concentrations in EPF samples. The retrieved studies involved more than 39 apparently healthy subjects. The ages of subjects were not presented. The information about analytical method was available for 2 studies. One study determined Na concentration by the traditional chemical analytical method,⁷¹ and other one using FES.⁷⁵

Table 6 presents the differences between the mean of Ca, Cl, K, Mg, and Na concentration in the prostatic fluid obtained by our review and the mean of these elements in blood serum, urine, breast milk, and mixed saliva of Reference Man.

Table 1 Reference data of Ca in normal human prostatic fluid

Reference	Meth.	n	Age	Treatment of samples	Ca, mg/L	
					M±SD	Range*
Huggins et al., ⁷¹	Chem	3	-	AD	1210	1150-1310
Burgos ⁷²	-	-	-	-	600	-
Homonnai et al., ⁷³	AAS	12	-	AD	1280±73	-
Zaneveld & Tauber ⁷⁴	-	-	-	-	1202	-
Kavanagh ⁷⁵	AAS	34	-	AD	802±305	289-1550
Daniels & Grayhack ⁷⁶	-	-	-	-	1200	-
Number of all references					6	
Median of means, mg/L					1201	
Range of means, mg/L					600-1280	

M—Arithmetic mean, SD—standard deviation of mean, Range*—range of individual results, Chem—traditional chemical method, AAS—atomic absorption spectrophotometry

Table 2 Reference data of Cl in normal human prostatic fluid

Reference	Meth.	n	Age	Treatment of samples	Cl, mg/L	
					M±SD	Range*
Huggins et al., ⁷¹	Chem	8	-	AD	1350	1230-1630
Burgos ⁷²	-	-	-	-	1350	-
Zaneveld & Tauber ⁷⁴	-	-	-	-	1347	-
Kavanagh ⁷⁵	Chem	38	-	AD	1370±650	500-3270
Daniels & Grayhack ⁷⁶	-	-	-	-	1350	-
Number of all references				5		
Median of means, mg/L				1350		
Range of means, mg/L				1347-1370		

M—arithmetic mean, SD—standard deviation of mean, Range*—range of individual results, Chem—traditional chemical method

Table 3 Reference data of K in normal human prostatic fluid

Reference	Meth.	n	Age	Treatment of samples	K, mg/L	
					M±SD	Range*
Huggins et al., ⁷¹	Chem	6	-	AD	1890	1120-2400
Burgos ⁷²	-	-	-	-	1170	-
Zaneveld & Tauber ⁷⁴	-	-	-	-	1877	-
Kavanagh ⁷⁵	FES	34	-	AD	2612±958	1110-6120
Daniels & Grayhack ⁷⁶	-	-	-	-	1880	-
Number of all references				5		
Median of means, mg/L				1880		
Range of means, mg/L				1170-2612		

M—arithmetic mean, SD—standard deviation of mean, Range*—range of individual results, Chem—traditional chemical method, FES—flame emission spectrophotometry

Table 4 Reference data of Mg in normal human prostatic fluid

Reference	Meth.	n	Age	Treatment of samples	Mg, mg/L	
					M±SD	Range*
Homonnai et al., ⁷³	AAS	12	-	AD	486±45	-
Zaneveld & Tauber ⁷⁴	-	-	-	-	486	-
Kavanagh ⁷⁵	AAS	34	-	AD	406±117	150-780
Daniels & Grayhack ⁷⁶	-	-	-	-	486	-
Number of all references				4		
Median of means, mg/L				486		
Range of means, mg/L				406-486		

M—arithmetic mean, SD—standard deviation of mean, Range*—range of individual results, AAS—atomic absorption spectrophotometry

Table 5 Reference data of Na in normal human prostatic fluid

Reference	Meth.	n	Age	Treatment of samples	Na, mg/L	
					M±SD	Range*
Huggins et al., ⁷¹	Chem	5	-	AD	3517	3426-3632
Burgos ⁷²	-	-	-	-	3586	-
Zaneveld & Tauber ⁷⁴	-	-	-	-	3517	-
Kavanagh ⁷⁵	FES	34	-	AD	3610±920	2530-7520
Daniels & Grayhack ⁷⁶	-	-	-	-	3517	-
Number of all references				5		
Median of means, mg/L				3517		
Range of means, mg/L				3517-3610		

M—arithmetic mean, SD—standard deviation of mean, Range*—range of individual results, Chem—traditional chemical method, FES—flame emission spectrophotometry

Table 6 The differences between the mean of Ca, Cl, K, Mg, and Na concentration in the prostatic fluid and in blood serum, urine, breast milk, and mixed saliva of Reference Man (mg/L)

Element	This work	Reference Man				Ratios			
	Prostatic fluid	Blood serum ⁸³	Urine ⁸³	Breast milk ⁸³	Mixed saliva ⁸⁴				
	1	2	3	4	5	1/2	1/3	1/4	1/5
Ca	1201	97	151	386	37	12.4	7.95	3.11	32.5
Cl	1350	3655	3350	563	288	0.37	0.4	2.4	4.69
K	1880	191	1870	685	416	9.84	1.01	2.74	4.52
Mg	486	21.7	81	36	7.9	22.4	6	13.5	61.5
Na	3517	3251	2907	168	52	1.08	1.21	20.9	67.6

Discussion

Samples of EPF are much more available for study than prostate tissue and can be obtained without damaging the prostate gland. Information about Ca, Cl, K, Mg, and Na 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. Thus, it dictates a need in reliable values for the Ca, Cl, K, Mg, and Na concentrations in the EPF of apparently healthy subjects ranging from young adult males to elderly persons.

The range of means of Ca concentration reported in the literature for normal EPF varies widely from 600mg/L⁷² to 1280mg/L⁷³ with median of means 1201mg/L (Table 1).

The range of means of Cl concentration reported in the literature for normal EPF varies from 1347mg/L⁷² to 1370mg/L⁷³ with median of means 1350mg/L (Table 2).

The range of means of K concentration reported in the literature for normal EPF varies widely from 1170mg/L⁷² to 2612mg/L⁷⁵ with median of means 1880mg/L (Table 3).

The range of means of Mg concentration reported in the literature for normal EPF varies from 406mg/L⁷⁵ to 486mg/L⁷⁶ with median of means 486mg/L (Table 4).

The range of means of Na concentration reported in the literature

for normal EPF varies from 3517mg/L⁷¹ to 3610mg/L⁷⁵ with median of means 3517mg/L (Table 5).

As indicated above, the range of means of Ca and K concentration reported in the literature for normal EPF varies widely. This can be explained by a dependence of some MEs content on many factors, including age, ethnicity, mass of the gland, diet, and others. Not all these factors were strictly controlled in cited studies. However, in our opinion, leading cause of inter-observer variability was insufficient quality control of results in these studies. In all reported papers the destructive analytical methods were used. The destructive analytical methods need in sample acid digestion under high temperature. There is evidence that by use of this treatment some quantities of MEs, including Ca and K, are lost.^{79–81} On the other hand; MEs 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 chemical elements, for complete acid digestion of the sample, and for the contaminations by chemical elements during sample decomposition, which needs adding some chemicals. It is possible to avoid these not easy procedures using non-destructive methods. For example, such method as energy dispersive X-ray fluorescence analysis (EDXRF) is a fully instrumental and nondestructive analytical tool because a drop of EPF is investigated without requiring any sample pretreatment or its consumption.⁸² It is, therefore, reasonable to conclude that the choice of analytical method and quality control of results are very important factors for using the MEs concentration in EPF as biomarker.

The obtained median of means for Ca concentrations in normal human prostatic fluid was at least one order of magnitude higher than mean values of the electrolyte content in blood serum and mixed saliva, and 8 and 3 times higher than in urine and breast milk, respectively (Table 6). The median of means for Mg concentrations in normal human prostatic fluid was at least one order of magnitude higher than mean values of the electrolyte content in blood serum, breast milk, and mixed saliva, and 6 times higher than in urine (Table 6). Thus, it was confirmed that the human prostatic secretion is a target fluid of human body for Ca and Mg.

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 49 normal controls were investigated from all 6 studies. As such, it is hard to make definitive conclusions about the clinical value of the Ca, Cl, K, Mg, and Na concentration in EPF as biomarker.

Conclusion

The present study is a comprehensive study regarding the determination of Ca, Cl, K, Mg, and Na concentration in EPF as a biomarker for the diagnostics of prostate disorders. The study has demonstrated that the human prostatic secretion is a target fluid of human body for Ca and Mg, because of small sample size and high heterogeneity of data for Ca and K, we recommend other primary studies.

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Conflicts of interest

The author declares that there are no conflicts of interest.

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