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REVIEW ARTICLE

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A Systematic Review of the Phosphorus Content of the Normal Human Prostate 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 diagnosis of prostate disorders has become progressively more complex and controversial. It was suggested that the P level in prostatic tissue plays an important role in prostatic carcinogenesis and its measurement may be useful as a cancer biomarker. These suggestions promoted more detailed studies of the P content in the prostatic tissue of healthy subjects. The present study evaluated by systematic analysis the published data for P content analyzed in prostatic tissue of "normal" glands. This evaluation reviewed 1919 studies, all of which were published in the years from 1921 to 2020 and were located 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 the measured P content in prostates of apparently healthy men. The objective analysis was performed on data from the 27 studies, which included 974 subjects. It was found that the range of means of prostatic P content reported in the literature for "normal" gland varies widely from 350 mg/kg to 2460 mg/kg with median of means 1295 mg/kg on a wet mass basis. The study has demonstrated that levels of P in "normal" prostates likely depends on androgen levels, dietary P intake, and relative amounts of different types of prostatic tissue studied, and does not depend on age and zone of human prostate sampled,. Finally, because of small sample size and high data heterogeneity, we recommend other primary studies be performed.

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Introduction

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

In our previous studies the significant involvement of some chemical elements, including trace elements (TEs), in the function of the prostate was found. [5-16]. Moreover, it was demonstrated that the changes of content as well as ratios of chemical elements in prostate tissue can be used as biomarkers [17-27]. Published data also shown that the intracellular disturbances of main electrolytes metabolism can play a significant role in etiology of cancer, including PCa [28,29]. Phosphorus (P) is not the exclusion, because high dietary levels of P have been linked to development of cancer in experimental and population-based study, particularly in men [30,31].

P is one of most important nutrients to the human body. It is required in the ATP formation, kinase/phosphatase signaling and in the synthesis of lipids, carbohydrates and nucleic acids. Furthermore, it plays a key role for normal skeletal and dentin mineralization [32]. As a common dietary element, P might modify the behavior of cells, including cellular growth and proliferation, the effects of P as well as all other main electrolytes and TEs are related to their concentration. Recorded observations range from a deficiency state, through normal function as biologically essential components, to an imbalance, when excess of one element interferes with the function of another, to pharmacologically active concentrations, and finally to toxic and even life-threatening concentrations [33]. Thus, adequate P intake is important for the maintenance of bone

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health, cellular function and general metabolism in the human body. However, adult Americans, for example, typically consume on average 1400 mg, or more, of P daily in meals, which almost doubles the recommended dietary allowance [34]. Moreover, the quantities of P continue to rise in the diet, in particular way in the western countries [34]. In this context, many chronic diseases, including cancer have been proposed to be associated with high P intakes and abundant P concentrations in fluids and tissues [35]. Recently, there have been a number of developments in the fields of P-induced carcinogenesis, however, precise molecular mechanisms by which this element causes healthy cells to transform to malignant states have yet to be fully defined. P homeostasis mechanisms are critically involved in both normal function and cancerous transformation of cells. Therefore, current models propose that dysregulated P homeostasis in cancerous cells depends on changes in the ratio of influx/efflux and storage of P, compared with normal cells, may contribute to P-induced carcinogenesis [34]. Homeostasis mechanisms of intra-prostatic P metabolism cause stable level of this element in normal functional conditions of the prostate. Thus, the P content in prostate tissue is an important parameter of the gland function.

By now, many studies have reported the P content in tissue of "normal" and affected glands. However, further investigation has been considered necessary to provide a practical reference data of P levels in prostate norm and disorders, because the findings of various studies indicate some discrepancies.

The present study addresses the significance of P levels in prostatic tissue as a biomarker of the gland's condition. Therefore, we systematically reviewed all the available relevant literature and performed a statistical analysis of P content in tissue of "normal" glands, which may provide 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 by consulting the Scopus, PubMed, MEDLINE, ELSEVIER-EMBASE, Cochrane Library, and the Web of Science databases, as well as from the personal archive of the author collected between 1966 to May 2020, using the key words: prostatic chemical elements, prostatic P content, prostatic TEs, and their combinations. For example, the search terms for P content were: "P mass fraction", "P content', "P level", "prostatic tissue P" and "P of prostatic tissue". The language of the article 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 for the each selected article were also evaluated for inclusion.

Eligibility Criteria

Inclusion Criteria

Only papers with quantitative data of P prostatic content were accepted for further evaluation. Studies were included if the control groups were healthy human males with no history or evidence of urological or other andrological disease and P levels were measured in samples of prostatic tissue.

Exclusion Criteria

Studies were excluded if they were case reports.

Data Extraction

A standard extraction of data was applied, and the following available variables were extracted from each paper: method of P determination, number and ages of healthy persons, sample preparation, mean and median of P levels, standard deviations of mean, and range of P levels. Abstracts and complete articles were reviewed independently, and if the results were different, the texts were checked once again until the differences were resolved.

Statistical Analysis

Studies were combined based on means of P levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of P contents. The objective analysis was performed on data from the 27 studies, with 974 subjects.

Results

Information about P levels in prostatic tissue in different prostatic diseases is of obvious interest, not only to understand the etiology and pathogenesis of prostatic diseases more profoundly, but also for their diagnosis, particularly for PCa diagnosis. Thus, it dictates a need for reliable values of the P levels in the prostatic tissue of apparently healthy subjects, ranging from young adult males to elderly persons.

A total of 1919 individual studies were identified. Among them 27 studies were ultimately selected according to eligibility criteria that investigated P levels in tissue of "normal" prostates (Table 1) and these 27 papers [9,13-14,36-59] comprised the material on which the review was based. A number of values for P mass fractions were not expressed on a wet mass basis by the authors of the cited references. However, we calculated these values using the medians of published data for water – 83% [44,60-62] and ash – 1% (on a wet mass basis) contents in normal prostates of adult men [38,44,63,64].

Table 1 summarizes general data from the 27 studies. The retrieved studies involved 974 subjects. The ages of subjects were available for 20 studies and ranged from 0–101 years. Information about the analytical method and sample preparation used was available for 23 studies. All studies determined P levels by destructive (require washing, pressing, cutting section on a cryomicrotome, high temperature drying, ashing, acid digestion, fixation in ethanol/chloroform/formaldehyde, and defatting of tissue samples) analytical methods (Table 1): one using atomic emission spectrometry (AES), one - atomic absorption spectrophotometry (AAS), one - synchrotron radiation-induced X-ray emission (SRIXE), one - total reflection X-ray fluorescence spectroscopy using synchrotron radiation technique (SR-TXRF), two – chemical, two - - inductively coupled plasma atomic emission spectrometry (ICPAES), and three – calorimetric measurement. In twelve studies a combination of neutron activation analysis (NAA) and ICPAES was used and results were summarized.

Table 1: Reference data of P mass fractions (mg/kg wet tissue) in "normal" human prostatic tissue

Reference	Method	n	Age, years M(Range)	Sample preparation	P	
					Mean±SD	Range
ICRP 1960 [36]	-	-	Adult	=	1100	-
Zakutinsky et al. 1962 [37]	-	-	Adult	-	1100	-
Tipton et al. 1963 [38]	AES	36	Adult	D, A	900±260	=
Hienzsch et al. 1970 [39]	Chemical	10	<1	A, AD	1173	-
		20	1-10	A, AD	1003	-
		20	11=30	A, AD	1088	-
		20	31-50	A, AD	964	-
		20	51-70	A, AD	1037	-
		20	71-90	A, AD	1020	-
Schneider et al. 1970 [40]	Calorimetric	21	16-37	A, AD	1088±136	-
Holm et al. 1971 [41]	Calorimetric	21	16-37	A, AD	1088±136	-
Forssen 1972 [42]	Calorimetric	12	Adult	A, AD	2460	1980-3000
Marezynska et al. 1983 [43]	Chemical	8	52(35-60)	FF,A,AD	1363±517	-
Woodard et al. 1986 [44]	-	-	-	-	1000	-
Oster et al. 1988 [45]	AAS	15	39(19-61)	AD	1300±300	-
ICRU 1992 [46]	-	-	-	-	2000	-
Kwiatek et al. 2005 [47]	SRIXE	1	-	CS (NB)	1000	-
Tohno et al. 2009 [48]	ICPAES	57(J)	65-101	F,FF,W,AD	816±1003	-
		13(T)	43-86	F,FF,W,AD	350±117	-
Zaichick et al. 2012 [49]	ICPAES	64	13-60	AD	1289±323	626-252
		9	13-20	AD	978±517	-
		28	21-40	AD	1321±338	-
		27	41-60	AD	1328±428	-
Zaichick et al. 2013 [9]	NAA+ICPAES	16	20-30	Intact, AD	1316±287	-
Leitao et al. 2014 [50]	SR-TXRF	8	18-30	AD	485±95	Med. 466
Zaichick et al. 2014 [51]	NAA+ICPAES	28	21-40	Intact, AD	1321±264	903-1819
		27	41-60	Intact, AD	1328±350	1015-2516
		10	61-87	Intact, AD	1210±391	1029-1527
Zaichick et al. 2014 [13]	NAA+ICPAES	16	20-30	Intact, AD	1316±287	-
Zaichick et al. 2014 [14]	NAA+ICPAES	50	0-30	Intact, AD	1400±380	-
		29	0-13	Intact, AD	1390±390	-
		21	14-30	Intact, AD	1400±390	-
Zaichick 2015 [52]	NAA+ICPAES	65	21-87	Intact, AD	1306±291	-
Zaichick et al. 2016 [53]	NAA+ICPAES	28	21-40	Intact, AD	1540±100	-
		27	41-60	Intact, AD	1660±120	-
		10	61-87	Intact, AD	1470±70	-
Zaichick et al. 2016 [54]	NAA+ICPAES	37	41-87	Intact, AD	1295±313	1015-2516
Zaichick et al. 2016 [55]	NAA+ICPAES	32	44-87	Intact, AD	1295±320	1015-2516
Zaichick et al. 2016 [56]	NAA+ICPAES	37	41-87	Intact, AD	1295±313	1015-2516
Zaichick et al. 2017 [57]	NAA+ICPAES	37	41-87	Intact, AD	1530±410	1120-2800
Zaichick 2017 [58]	NAA+ICPAES	37	41-87	Intact, AD	1295±313	1015-2519
Zaichick et al. 2019 [59]	NAA+ICPAES	37	41-87	Intact, AD	1295±313	1015-2519
Median of means Range of means (M_{min} - M_{max}), Ratio Mmax/Mmin All references		1295 350 – 2460 7.03 27				

M – arithmetic mean, SD – standard deviation of mean, AES – atomic emission spectrometry, AAS – atomic absorption spectrophotometry, SRIXE – synchrotron radiation-induced X-ray emission, NAA – neutron activation analysis, ICPAES – inductively coupled plasma atomic emission spectrometry, SR-TXRF – total reflection X-ray fluorescence spectroscopy using synchrotron radiation technique,

D – drying at high temperature, A – ashing, AD – acid digestion, FF – defatted (fat free), CS – cut section on a cryomicrotome, F – fixed in ethanol, chloroform, formaldehyde, W – washing, NB – needle biopsy, J – Japanese, T – Thai.

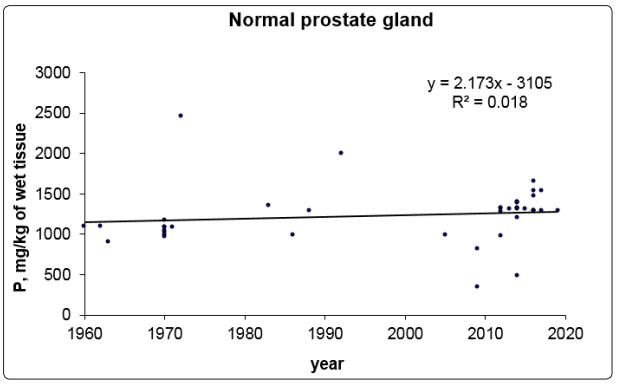

Figure 1: Data on P content in "normal" prostate tissue reported from 1960 to 2020.

Discussion

The range of means of P mass fractions reported in the literature for "normal" prostatic tissue varies widely from 350 mg/kg [45] to 2460 mg/kg [52] with median of means 1295 mg/kg wet tissue (Table 1). Thus, the maximal value of mean P mass fraction reported in the literature was 7.03 times higher the minimal value of mean P mass fraction. This variability of reported mean values can be explained by a dependence of P content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, non-homogeneous distribution of P levels throughout the prostate gland volume, age, ethnicity, diet, and others. Not all these factors were strictly controlled in the cited studies. For example, in some studies the "normal" prostate means a gland of an apparently healthy man who had died suddenly, but without any morphological confirmation of "normality" of his prostatic tissue. In other studies the "normal" prostate means a non-cancerous prostate (but hyperplastic and inflamed glands were included) and even a visually normal prostatic tissue adjacent to a prostatic malignant tumor. Some researchers used as the "normal" prostate the glands of patients who died from acute and chronic non-prostatic diseases including subjects who had suffered from prolonged wasting illnesses. In some studies whole glands were used for the investigation while in others the P content was measured in pieces of the prostate. Therefore published data allowed us to estimate the effect of only some different factors on P content in "normal" prostate tissue.

Analytical Method

Prostate tissue P contents showed large variations among published data. In our opinion, the leading cause of inter-observer variability was insufficient quality control of results in published studies. In many reported papers such destructive analytical methods as AES, AAS and ICP-AES were used. These methods require ashing or acid digestion of the samples at a high temperature. There is evidence that use of this treatment causes some quantities of P to be lost [33,65,66]. On the other hand, the P content of chemicals used for acid digestion can contaminate the prostate samples. Thus, when using destructive analytical methods it is necessary to allow for the losses of chemical elements, for example when there is complete acid digestion of the sample. Then there are contaminations by chemical elements during sample decomposition, which require addition of some chemicals.

Such analytical methods as SRIXE and SR-TXRF need to use thin sections of prostatic tissue. In the case of a frozen tissue samples, prostatic fluid may be lost as a result of cutting microscopic sections. And, besides, P, particularly from prostatic fluid, may be lost during sample fixation in ethanol/chloroform/formaldehyde.

It is possible to avoid these problems by using non-destructive methods. Such method NAA can be fully instrumental and nondestructive analytical tool because a tissue sample is investigated without requiring any sample pretreatment or its destruction.

It is, therefore, reasonable to conclude that the choice of analytical method and quality control of results are very important factors for using the P content in prostatic tissue as biomarkers.

Age

In a few studies a variation in P content with increasing of age was investigated by the comparison of different age groups or the Pearson's coefficient of correlation between age and P content in prostate tissue [9,13,14,39,48,49,51-53]. No significant direct or inverse correlations between age and P contents in "normal" prostate were found. However, elevated mass fractions of P (>4000 mg/kg wet tissue) were contained in one fourth of the prostates of Japanese over 70 years of age [48]. This level (>4000 mg/kg wet tissue) was almost 5 times higher than mean value of P content in the prostates of Japanese aged 65-101 years.

Androgen-Dependence of Prostatic P Levels

The lack of difference between prostatic P levels before and after puberty [14,39] allowed us to conclude that in man androgens does not govern this element's content of the prostate. However, Wulaningsih et al. [67] findings suggest a weak link among sex hormones and P in men.

Uniform Distribution of P Within the Glandular Volume

The publications on distribution of P within the glandular volume were not found. The trend line of P content data in normal prostate (Figure 1) did not indicated a visible difference between results obtained during periods 1960-1992 and 2005-2019 years. In all studies published in 1960-1992 years the whole glands were used for the prostatic P content investigations, while peripheral zones of prostates were mainly involved for this purpose in the recent investigations. It is, therefore, reasonable to conclude that there is the uniform distribution of P within the glandular volume.

Variable Distribution of P between the Different Components of Prostatic Tissue

According to Deering et al. [68], prostatic tissue contains three main components: glandular epithelium, prostatic fluid contained in the glandular lumina, and fibromuscular tissue or stroma. Studies on the P content in epithelium and stroma that was separated from each other were not found. However, the P concentrations in prostatic fluid have been investigated in Huggins et al. study [69]. It has been found that the mean value of P concentration in the prostatic fluid equals 33.8 mg/dm3. This level of prostatic fluid P is almost 40 times lower than P concentrations in prostate tissue (Table 1). From this it follows that the cellular components of prostate are the main pool for P.

Dietary P

Because significant correlations between high P intake and the risk of cancer, including PCa, have been reported [70], it is possible

hypothesized that dietary P intakes affect the element's levels in the prostate. There are data that support this hypothesis. For example, according to Tohno et al. [48] the mean P mass fraction in the Japanese prostates (816 mg/kg wet tissue) was 2.3 times higher than in the Thai prostates (350 mg/kg wet tissue). Likely, the differences in dietary preferences of Thai and Japanese subjects may well explain this difference.

Thus, according our study no one influencing factor could explain the variability of published means for prostatic P levels from 350 mg/kg to 2460 mg/kg in wet tissue. It is, therefore, reasonable to assume from data of our study that inaccuracy of analytical technologies employed caused so great variability of published means for prostatic P levels. This conclusion was supported the fact that the Certified Reference Materials for quality control of results were used only in a very few reported studies. Anyway, the median of means for prostatic P obtained by us in the present review (1295 mg/kg wet mass basis) is significantly differ than data of the report 89 of ICRP (2000 mg/kg wet mass basis) [71]. Thus, the data shown in Table 1 suggest that P mass fractions in prostate tissue of the ICRP Reference Man need revision.

There are some limitations in our study, which need to be taken into consideration when interpreting the results of this review. The sample size of each study was sometimes relatively small (from 1 to 110), and a total of 974 normal controls were investigated from all 27 studies. As such, it is hard to draw definite conclusions about the reference value of the P content in "normal" prostate as well as about the clinical value of the Ca levels in "normal" prostates as a biomarker.

Conclusion

The present study is a comprehensive study regarding the determination of P content in "normal" human prostates. With this knowledge P levels may then be considered as a biomarker for the recognition of prostate disorders. The study has demonstrated that levels of P in "normal" prostates likely depends on androgen levels, dietary P intake, and relative amounts of different types of prostatic tissue studied, and does not depend on age and zone of human prostate sampled. Because of the uncertainties we have outlined, we recommend other primary studies be performed.

Conflict of Interest

The author declares that there no conflict of interest.

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