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A systematic review of the arsenic content of the normal human prostate gland

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Abstract
Background: The prostate gland is subject to various disorders. The etiology and pathogenesis of these diseases remain 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 arsenic (As) 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 As content in the prostatic tissue of healthy subjects.
Objective: The present study evaluated by systematic analysis the published data for as content analyzed in prostatic tissue of "normal" glands.
Methods: This evaluation reviewed 1927 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 As content in prostates of apparently healthy men. The objective analysis was performed on data from the 16 studies, which included 471 subjects.
Results: It was found that the range of means of prostatic as content reported in the literature for "normal" gland varies widely from 0.00039 mg/kg to <0.017 mg/kg with median of means 0.0031 mg/kg on a wet mass basis.
Conclusion: Because of small sample size and high data heterogeneity, we recommend other primary studies be performed.

Keywords: Arsenic, human prostate, normal prostatic tissue, biomarkers

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 remain not well understood. A better understanding of the etiology and causative risk factors are essential for the primary prevention of these diseases.

In our previous studies the significant involvement of trace elements (TEs) in the function of the prostate was found [4-15]. It was also shown that levels of TEs in prostatic tissue can play a significant role in etiology of PCa [16-19]. Moreover, it was demonstrated that the changes of some TE levels, including arsenic (As), and TE content ratios in prostate tissue can be used as biomarkers [20-27].

The effects of TEs, including as, 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 [28]. In this context, a significant dose-response relation was observed between low-level as exposure and cancers of the bladder, kidney, skin, and lung in both males and females, and cancers of the prostate and liver in males [29]. Recent available evidence in human populations and human cells *in vitro* indicates that the prostate is a target for As carcinogenesis. A role for this common environmental contaminant in human PCa initiation and/or progression would be very important [30-36].

By now, an exceedingly scant literature exists on quantitative As content in tissue of "normal" and affected glands. The analyses reported are few in number, incomplete and difficult to interpret. Moreover, the findings of various studies indicate some discrepancies.

The present study addresses the significance of as 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 as 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 May 1966 to September 2020, using the key words: prostatic trace elements, prostatic As content, prostatic tissue, and

their combinations. For example, the search terms for as content were: "As mass fraction", "As content", "As level", "prostatic tissue as" and "As 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 as 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 Andrologia disease and as levels were measured in samples of prostatic tissue.

Exclusion criteria

Studies were excluded if they were case reports. Studies involving persons from as contaminated area and subjects that were as occupational exposed were also excluded.

Data extraction

A standard extraction of data was applied, and the following available variables were extracted from each paper: method of As determination, number and ages of healthy persons, sample preparation, mean and median of As levels, standard deviations of mean, and range of As 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 as levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of as contents. The objective analysis was performed on data from the 16 studies, with 471 subjects.

Results

Information about as 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 and PCa risk prognosis [27]. Thus, it dictates a need for reliable values of the As levels in the prostatic tissue of apparently healthy subjects, ranging from young adult males to elderly persons.

Possible publications relevant to the keywords were retrieved and screened. A total of 1927 publications were primarily obtained, of which 1911 irrelevant papers were excluded. Thus, 16 studies were ultimately selected according to eligibility criteria that investigated as levels in tissue of "normal" prostates (Table 1) and these 16 papers [9, 13, 14, 27, 37-48] comprised the material on which the review was based. A number of values for as 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% [49-52] and ash – 1% (on a wet mass basis) contents in "normal" prostates of adult men [51, 53-55].

Table 1 summarizes general data from the 16 studies. The retrieved studies involved 471 subjects. The ages of subjects were available for 10 studies and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 15 studies. Six studies determined as levels by destructive (require high temperature drying, acid digestion, fixation in ethanol/chloroform/formaldehyde, and paraffin/resin embedding of tissue samples) analytical methods (Table 1): one using atomic absorption spectrophotometry (AAS), two - inductively coupled plasma mass spectrometry (ICPMS), and three – radiochemical neutron activation analysis (RNAA). One study detected as level in intact prostatic tissue samples by nondestructive analytical method, such as instrumental neutron activation analysis (INAA). In eight studies a combination of destructive (ICPMS) and nondestructive (INAA) methods was used and results were summarized.

Discussion

The range of means of as mass fractions reported in the literature for "normal" prostatic tissue varies widely from 0.00039 mg/kg [27] to <2.9 mg/kg [37] with median of means <0.0031 mg/kg wet tissue (Table 1). The maximal value of mean as mass fraction reported [37] was 935 times higher the median of as mass fraction means and at least two orders of magnitude higher than all other published means. Thus, value <2.9 mg/kg [37] can be excluded. However, without this result range of means of as mass fractions for "normal" prostatic tissue remains very wide from 0.00039 mg/kg [27] to <0.017 mg/kg [38] with the same median of means <0.0031 mg/kg wet tissue and H_{max}/M_{min} ratio approximately 44 (Table 1).

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

Reference	Method	n	Age, years Range	Sample preparation	As	
					Mean±SD	Range
Zakutinsky *et al*.1962 [37]	-	-	-	-	**<2.9**	-
Smith 1967 [38]	RNAA	10	Adult	D	0.0077	0.0017-0.0153
Liebscher *et al*.1968 [39]	RNAA	10	Adult	D	0.0077±0.0037	0.0017-0.0153
Smith 1970 [40]	RNAA	10	Adult	D	0.0077±0.0037	0.0017-0.0153
Zaichick *et al*. 2012 [41]	ICP-MS	64	13-60	AD	≤0.0031	<0.0017-0.0275
Zaichick *et al*. 2013 [9]	2 methods	16	0-30	Intact, AD	≤0.012	-
Neslund-Dudas	ICP-MS	21	Adult, NS	F,P,AD,NB	0.00092	-
et al 2014 [42]		25	Adult, ES	F,P,AD,NB	0.00087	-
Zaichick *et al*. 2014 [13]	2 methods	16	0-30	Intact, AD	≤0.017	-
Zaichick *et al*. 2014 [43]	2 methods	28	21-40	Intact, AD	≤0.0020	<0.0017-0.0034

		27	41-60	Intact, AD	≤0.0044	<0.0017-0.027
		10	61-87	Intact, AD	0.0020	0.0017-0.0034
Zaichick *et al*. 2014 [14]	2 methods	16	0-30	Intact, AD	≤0.012	-
Zaichick *et al*. 2015 [44]	INAA	32	44-87	Intact	≤0.017	-
Zaichick 2015 [45]	2 methods	65	21-87	Intact, AD	≤0.0031	-
Zaichick *et al*. 2017 [46]	2 methods	37	41-87	Intact, AD	0.003	-
Zaichick 2017 [47]	2 methods	37	41-87	Intact, AD	≤0.0031	-
Singh *et al*. 2018 [27]	AAS	10	Adult	AD	0.00039±0.00034	-
Zaichick *et al*. 2019 [48]	2 methods	37	41-87	Intact, AD	≤0.0031	-
Median of means		0.0031 or 0.0031 (without <2.9)				
Range of means (M_{min} - M_{max}),		0.00039 - <2.9 or 0.00039 –< 0.017 (without <2.9))				
Ratio M_{max}/M_{min}		<2.9/0.00039=<7436 or <0.017/0.00039=<43.6 (without <2.9)				
All references		16				

M – arithmetic mean, SD – standard deviation of mean,
RNAA – radiochemical neutron activation analysis, ICPMS – inductively coupled plasma mass spectrometry; INAA – instrumental neutron activation analysis, AAS – atomic absorption spectrophotometry, 2 methods –INAA+ICPMS.NS – never-smokers, ES– ever-smokers, D – drying at high temperature, AD – acid digestion, F – fixed in ethanol/chloroform/formaldehyde, P –paraffin embedded, NB – needle biopsy.

This variability of reported mean values can be explained by a dependence of As content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, possible non-homogeneous distribution of As levels throughout the prostate gland volume, age, ethnicity, diet, smoking, alcohol intake, consuming supplemental Zn and Se, 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. In some studies whole glands were used for the investigation while in others the As content was measured in pieces of the prostate. However, the very short list of published data does not allowed us to estimate the effect of these factors on As content in "normal" prostate tissue.

In our opinion, the leading cause of inter-observer As content variability was insufficient quality control of results in published studies. Almost in all reported papers such destructive analytical methods as RNAA, AAS and ICPMS were used. These methods require acid digestion of the samples at a high temperature. There is evidence that use of this treatment causes some quantities of TEs to be lost [28, 56, 57]. Particularly, it concerns such volatile chemical element as As. On the other hand, the As 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 TEs, for example when there is complete acid digestion of the sample. Then there are contaminations by TEs during sample decomposition, which require addition of some chemicals. In the case of a paraffin/epoxy embedded tissue samples As, 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, but up to now there are no analytical methods which allow to quantify As content in "normal" prostate without acid digestion of the samples at a high temperature. It is, therefore, reasonable to conclude that the quality control of results is very important factor for using the As content in prostatic tissue as biomarkers.

All natural chemical elements of the Periodic System, including As, present in all subjects of biosphere [28, 58, 59]. During the long evolutional period intakes of As in organisms were more or less stable and organisms were adopted for such environmental conditions. Moreover, organisms, including human body, involved low doses of this element in their functions [60, 61]. As minerals have been known and used in relative small amounts since ancient times. As was frequently included in bronze, and used in medicine, cosmetics, and for murder.The situation began to change after the industrial revolution, particularly, over the last 100 years. The primary use of As is in industry, for example, in car batteries and ammunition, semiconductor electronic devices, optoelectronics, wood products as a wood preservative, pigments for plastics, ceramics and glasses. This metalloid is widely used in agriculture as pesticides, herbicides, and insecticides, as well as a feed additive in poultry and swine production. Its compounds are also used in medicine and military.

Thus, inorganic As is ubiquitously distributed in environment and food, water, and air everywhere contain this element. In addition to the abundant natural sources of As, there are a large number of industrial and agricultural sources of As to the soil (through atmospheric emissions originating from residues from coal, oil, and gas combustion, urban refuse, mine tailings, Au, Cu, and Pb smelter slag, waste, including pharmaceutical waste, smelting activities to phosphate fertilizers, and also form pesticides, herbicides, insecticides, and seaweed fertilizers application), water (through irrigation and industrial liquid waste, livestock dips, and wastewater sludge application), and air (through atmospheric industrial emissions) contamination. From the polluted environment As is subsequently introduced into the food chain [62]. However, the major source of human exposure to As on unpolluted territories is naturally contaminated drinking water from underground wells [28-30, 33, 34, 36].

Commercially, As is produced as As trioxide or as a pure element, however, these have not been produced in the United States since 1985. As trioxide is obtained as a byproduct from dusts and residues produced during the treatment of Au, Cu and Pb metal ores. China is the world's leading producer of arsenic (25,000 tons in 2014) followed by Chile (10,000 tons), Morocco (8,000 tons), Russia (1,500 tons), Belgium (1,000 tons), Bolivia (52 tons), and Japan (45 tons). Since the use of As is linked to the rapidly developing modern technology, we can assume that over

the years, the need of industry in this metalloid has increased significantly and would continue to increase in the future. Published data showed an increase in As level for fluids and tissue of human body as the As intake increased [63-66]. Thus, we can conclude that the human body burden of As, including prostate tissue, has increased over the last 100 years due to an increase in global environmental As pollution [67]. It is likely that this tendency will continue.

As mentioned above, an ingestion of As by humans can cause a variety of disorders, such as skin lesions, problems with the respiratory and/or nervous systems, and different types of cancers, including PCa. Significant correlations between as exposure and the risk of PCa have been reported [29-36]. However, precise molecular mechanisms by which this metalloid causes healthy cells to transform to malignant states have yet to be fully defined. Kim *et al* [32]. reported that inorganic As induces apoptosis, necrosis, and autophagy in the studied prostate cancer cell lines and suggest that this effect could be via a reactive oxygen species (ROS)-dependent mechanism. Tokar *et al* [68]. showed that As can transform prostate epithelial stem cells into cancerous stem cells. Recent studies also reported the ability of As malignantly transforming human prostate epithelial cells via epigenetic alterations, such as miRNA dysregulation [69], silencing of mismatch repair gene MLH1 expression [70] while altering the expression of DNA methyl trans ferases such as DNMT1, DNMT3a, MeCP2, MBD1, and MBD4 [70, 71], and also genetic changes such as gene amplification leading to the overexpression of KRAS [72, 73].

Thus, according our study for unpolluted areas there are no information could explain the variability of published means for "normal" prostatic As levels from 0.00039 mg/kg to <0.017 mg/kg in wet tissue. Moreover, prostate tissue as contents showed large variations among individuals, but sources of the variation remain unknown. 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 as 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.

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 10 to 65), and a total of 471 "normal" prostates were investigated from all 16 studies. As such, it is hard to draw definite conclusions about the reference value of the As content in "normal" prostate as well as about the clinical value of the As levels in "normal" prostates as a biomarker.

Conclusions

The present study is a comprehensive study regarding the determination of as content in "normal" human prostates. With this knowledge as levels may then be considered as a biomarker for the recognition of prostate disorders. The study has demonstrated that levels of as in "normal" prostates depends on many unknown factors. Because of the uncertainties we have outlined, we recommend other primary studies be performed.

Competing Interests

Author has declared that no competing interests exist. The author alone is answerable for the substance and composing of the paper.

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