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Review

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A Systematic Review of the Antimony 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 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 antimony (Sb) 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 Sb content in the prostatic tissue of healthy subjects. The present study evaluated by systematic analysis the published data for Sb content analyzed in prostatic tissue of "normal" glands. This evaluation reviewed 1998 studies, all of which were published in the years from 1921 to 2020 and were located by searching the databases PubMed, Scopus, 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 Sb content in prostates of apparently healthy men. The objective analysis was performed on data from the 23 studies, which included 1173 subjects. It was found that the range of means of prostatic Sb content reported in the literature for "normal" gland varies widely from 0.0066 mg/kg to 0.071 mg/kg with median of means 0.0085 mg/kg on a wet mass basis. 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 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, including antimony (Sb), can play a significant role in etiology of PCa [16-20]. Moreover, it was demonstrated that the changes of some TE levels and Zn/Sb ratios in prostate tissue can be used as biomarkers [21-27].

It was indicated low levels of Sb in human prostatic tissue (0.071 mg/kg of wet tissue) in studies published more than 50 years ago [28]. This finding allowed conclude that the prostate gland accumulates Sb, because the levels of metalloid in prostates was almost four orders of magnitude higher the blood serum reference level (0.00001 mg/L) and one order of magnitude higher the liver reference level [29]. Furthermore, experimental and epidemiological data identified that Sb compounds should be considered as genotoxic carcinogens [30-34]. Consequently, the International Agency for Research on Cancer (IARC) has evaluated Sb as possibly carcinogenic to humans (Group 2B) [35]. These findings promoted more detailed studies of the Sb content of prostatic tissue of healthy subjects, as well as of patients with different prostatic diseases, including BPH and PCa.

The effects of TEs, including Sb, 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 [36-38]. In this context, for example, low dose of Sb has some useful effects on health, but significant exposure to this metalloid may result in adverse health effects in different organs or tissues, including malignancy such as Non-Hodgkin's lymphoma and melanoma, cancer of the lung, colon, rectum, bladder, thyroid, pleura, testis and PCa [31-34]. However, it still remains unclear what precise mechanism is responsible for Sb genotoxicity [30,39].

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

The present study addresses the significance of Sb 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 Sb 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 PubMed, Scopus, ELSEVIER-EMBASE, Cochrane Library, and the *Web of Science* databases, as well as from the personal archive of the author collected between 1966 to 2020, using the key words: prostatic trace elements, prostatic Sb content, prostatic tissue, and their combinations. For example, the search terms for Sb content were: "Sb mass fraction", "Sb content", "Sb level", "prostatic tissue Sb" and "Sb 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 Sb 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 Sb levels were measured in samples of prostatic tissue.

Exclusion Criteria

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

Data Extraction

A standard extraction of data was applied, and the following available variables were extracted from each paper: method of Sb determination, number and ages of healthy persons, sample preparation, mean and median of Sb levels, standard deviations of mean, and range of Sb 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 Sb levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of Sb contents. The objective analysis was performed on data from the 23 studies, with 1173 subjects

Results

Information about Sb 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 [27,36]. Thus, it dictates a need for reliable values of the Sb 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 1998 publications were primarily obtained, of which 1975 irrelevant papers were excluded. Thus, 23 studies were ultimately selected according to eligibility criteria that investigated Sb levels in tissue of normal prostates (Table 1) and these 23 papers [7,9,11,13,14,24,26,28,40-54] comprised the material on which the review was based.

A number of values for Sb 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% [55-58] and ash – 1% (on a wet mass basis) contents in normal prostates of adult men [57,59-61].

Table 1 summarizes general data from the 23 studies. The retrieved studies involved 1173 subjects. The ages of subjects were available for 20 studies and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 22 studies. One study determined Sb levels by inductively coupled plasma mass spectrometry (ICPMS) (Table 1). ICPMS is the destructive analytical method, because it requires sample acid digestion. Nine studies detected Sb level in intact prostatic tissue samples by nondestructive analytical method, such as neutron activation analysis (NAA). In twelve studies a combination of destructive and nondestructive methods (ICPMS and NAA) was used and results were summarized.

Figure 1 illustrates the data set of Sb measurements in 23 studies during the period from 1962 to 2020.

Discussion

The range of means of Sb mass fractions reported in the literature for "normal" prostatic tissue varies widely from 0.0066 mg/kg [45] to <2.9 mg/kg [40] with median of means 0.0085 mg/kg wet tissue (Table 1). The maximal value of mean Sb mass fraction reported [40] was 341 times higher the median of Sb mass fraction means and at least one order of magnitude higher than all other published means. Thus, value <2.9 mg/kg [40] can be excluded. However, without this result range of means of Sb mass fractions for "normal" prostatic tissue remains very wide from 0.0066 mg/kg [45] to 0.071 mg/kg [28] with median of means 0.0085 mg/kg wet tissue and M_{max}/M_{min} ratio approximately 11 (Table 1).

This variability of reported mean values can be explained a priori by a dependence of Sb content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, possible non-homogeneous distribution of Sb levels throughout the prostate gland volume, age, ethnicity, diet, smoking, alcohol intake, consuming supplemental trace elements, and others. Not all these factors were strictly controlled in the cited studies. For example, in some studies the

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

Reference	Method	n	Age, range years	Sample preparation	Sb	
					M±SD	M±SD
Zakutinsky et al. 1962 [40]	-	-	Adult	-	<2.9	-
Smith 1967 [28]	NAA	7	Adult	D	0.071	0.0051-0.275
Liebscher et al. 1968 [41]	NAA	7	Adult	D	0.071±0.095	0.0051-0.275
Zaichick et al. 2011 [42]	NAA	64	13-60	Intact	0.0085±0.0063	0.00085-0.027
		9	13-20	Intact	0.0083±0.0061	-
		28	21-40	Intact	0.0094±0.0060	-
		27	41-60	Intact	0.0078±0.0068	-
Zaichick et al. 2012 [24]	NAA	37	66±8	Intact	0.0077±0.0063	0.00078-0.027
Zaichick et al. 2012 [43]	ICPMS	64	13-60	AD	0.0068±0.0063	0.00136-0.027
Zaichick et al. 2013 [7]	NAA	29	0-13	Intact	0.0107±0.0092	-
		21	14-30	Intact	0.0088±0.0043	-
Zaichick et al. 2013 [9]	2 methods	16	20-30	Intact, AD	0.0087±0.0065	-
Zaichick et al. 2014 [44]	NAA	28	21-40	Intact	0.0094±0.0058	0.00153-0.027
		27	41-60	Intact	0.0078±0.0070	0.00078-0.027
		10	61-87	Intact	0.0068±0.0036	0.00187-0.0121
Zaichick et al. 2014 [45]	2 methods	28	21-40	Intact, AD	0.0077±0.0053	0.00153-0.027
		27	41-60	Intact, AD	0.0075±0.0068	0.0017-0.027
		10	61-87	Intact, AD	0.0066±0.0044	0.00136-0.015
Zaichick et al. 2014 [11]	2 methods	16	20-30	Intact, AD	0.0068±0.0036	-
Zaichick et al. 2014 [13]	NAA	29	0-13	Intact	0.014±0.012	-
		21	14-30	Intact	0.010±0.005	-
		50	0-30	Intact	0.0121±0.0094	-
Zaichick et al. 2014 [14]	2 methods	50	0-30	Intact, AD	0.0108±0.0087	-
		29	0-13	Intact, AD	0.013±0.011	-
		21	14-30	Intact, AD	0.0086±0.0049	-
Zaichick et al. 2015 [46]	NAA	32	44-87	Intact	0.0068±0.0054	0.00078-0.027
Zaichick 2015 [47]	2 methods	65	21-87	Intact, AD	0.0073±0.0058	-
Zaichick et al. 2016 [48]	NAA	37	41-87	Intact	0.0077±0.0063	0.00078-0.027
Zaichick et al. 2016 [49]	2 methods	28	21-40	Intact, AD	0.0092±0.0063	-

		27	41-60	Intact, AD	0.0091±0.0088	-
		10	61-87	Intact, AD	0.0084±0.0060	-
		37	41-87	Intact, AD	0.0089±0.0013	-
		65	21-87	Intact, AD	0.0091±0.0070	-
Zaichick et al. 2016 [50]	2 methods	32	44-87	Intact, AD	0.0066±0.0058	-
Zaichick et al. 2016 [51]	2 methods	37	41-87	Intact, AD	0.0073±0.0061	-
Zaichick et al. 2017 [26]	2 methods	37	41-87	Intact, AD	0.0073±0.0061	-
Zaichick et al. 2017 [52]	2 methods	37	41-87	Intact, AD	0.0085±0,0071	0,0015-0,0305
Zaichick 2017 [53]	2 methods	37	41-87	Intact, AD	0.0073±0.0062	0.00136-0.027
Zaichick et al. 2019 [54]	2 methods	37	41-87	Intact, AD	0.0073±0.0062	0.00136-0.027
Median of means		0.0085				
Range of means (M_{min} - M_{max}),		0.0066 – 2.90				
Ratio M_{max}/M_{min}		(<2.90/0.0066) = <439				
All references		23				

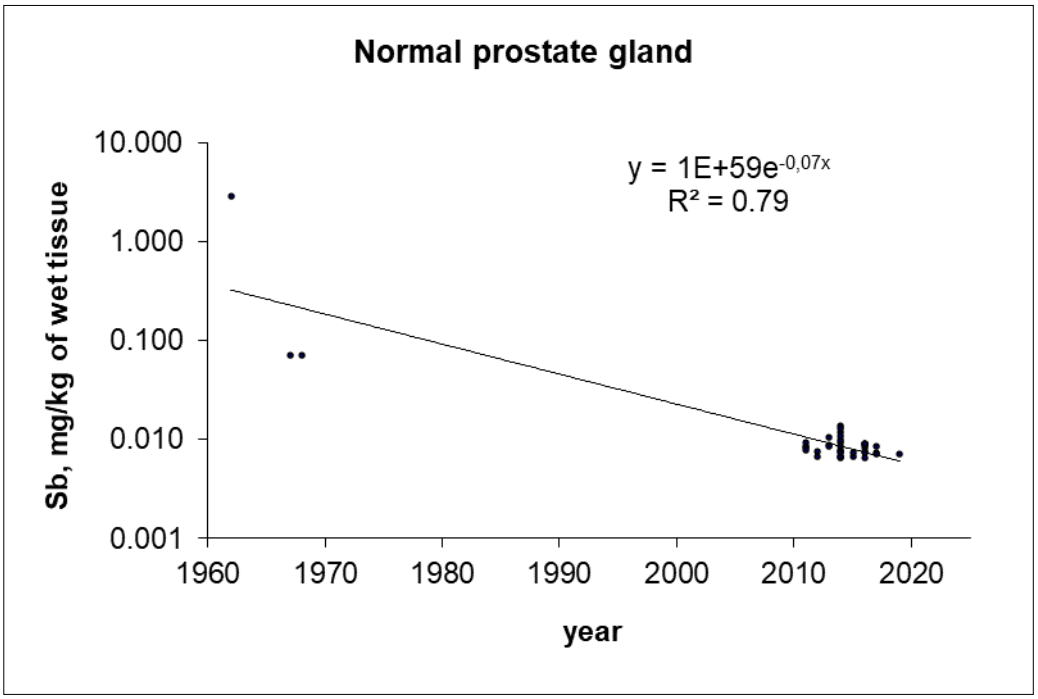

Figure 1. Data on Sb content in "normal" prostate tissue reported from 1962 to 2020.

"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 Sb content was measured in pieces of the prostate. Therefore published data allowed us to estimate the effect of only some different factors on Sb content in "normal" prostate tissue.

Analytical Method

The trend line of Sb content data in "normal" prostate (Figure 1) showed that an improvement of analytical technologies during last 50 years impacted significantly on the mean and variability of reported values. In our opinion, the leading cause of inter-observer variability was an insufficient sensitivity of analytical techniques and a lack of quality control of results in old studies published in 60s.

In one reported paper such destructive analytical method as ICP-MS was used. This method requires 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 [36,62,63]. On the other hand, the Sb 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. It is possible to avoid these problems by using non-destructive methods, such as NAA, which allow to quantify Sb content in "normal" prostate without acid digestion. Moreover, a good agreement between results obtained by both NAA and ICPMS methods under a strong quality control [9,11,14,26,45,47,49-54] shoved that in case of Sb it is possible to avoid uncertainties connected with acid digestion. It is, therefore, reasonable to conclude that the quality control of results is very important factor for using the Sb content in prostatic tissue as biomarkers.

Age

In a few studies which used the comparison of different age groups or the Pearson's coefficient of correlation between age and Sb content in prostate tissue it was not found a significant changes in Sb content with increasing age [7,13,14,42,44,45,49]. These findings allowed us to conclude that the Sb content in "normal" prostates does not depend on age.

Androgen-Independence of Prostatic Sb Levels

There was not found a significant difference between Sb levels in prostates of teenagers before puberty and of post-pubertal teenagers and young adults [7,13,14]. These findings allowed us to conclude that the Sb content in "normal" prostates does not depend on the level of androgens, and vice versa. However, studies on the association between the Sb content in "normal" prostates and the level of androgens in blood were not found.

Sb Intake

The general population can be exposed to low levels of Sb pri-marily through ingestion of drinking water and to a lesser degree through consumption of food and inhalation of ambient air [64]. One may also be exposed to Sb through skin contact with Sb alloys used in lead storage batteries, solder, sheet and pipe metal, bearings, castings, type metal, ammunition, pewter, paints, glass, pottery and ceramics [65]. Meats, vegetables, and seafood generally contain from 0.0002 to 0.0011 mg Sb per kg of fresh mass and on average, 0.005 mg Sb is consumed with food everyday [64]. Concentration of Sb in waters of different types such as tap water, household wells, groundwater, and surface waters variate very widely but the Sb drinking water limit is 0.005 mg/L [66]. However, most Sb concentrations in drinking water are below the 0.001 mg/L, except for some bottled waters that can show higher level under extended conditions of storage which promote Sb leaching from bottle plastic (polyethylene terephthalate - PET or "terylene) [64,67]. Sb poisoning may be resulted from drinking acidic fruit juices containing Sb oxide dissolved from the glaze of cheap enamelware containers [68'. Elevated Sb intake may also result from tobacco smoking because a cigarette

smoke contains significant amounts of this metalloid. In one study the Sb content was reported to be about 10 mg/kg in tobacco, 35-60 mg/kg in smoke condensate, and about 12-20 mg/kg in cigarette ashes [60]. Other potential sources of Sb exposure are medications, such as tartar emetic (Sb and potassium tartrate), used to induce vomiting and in treatment of helminthic and fungal infestations [70,71].

Sb Content in Body Fluids, Tissues and Organs

It is known that Sb is accumulated primarily in liver, kidney, skeleton, thyroid, and muscle [72]. For example, mass fraction of this metalloid in liver and kidney cortex of the persons from the reference group were 0.007 and 0.005 mg/kg of wet tissue respectively [69]. The median of prostatic Sb content means obtained in the present review (0.0085 mg/kg of wet tissue) is higher the metalloid level in liver. Thus, we can conclude that the prostate is also a target organ for Sb. A small increase of Sb intake for a long period associated with a great increase of metalloid concentration in blood [67,70], and, as a consequence in different organs, including the prostate.

All natural chemical elements of the Periodic System, including Sb, present in all subjects of biosphere [36,73,74]. During the long evolutional period intakes of Sb in organisms were more or less stable and organisms were adopted for such environmental conditions. Sb minerals have been known and used in relative small amounts since ancient times. Sb minerals were used in cosmetics, medicine, and for murder. Nicolas Lémery, a French chemist, was the first person to scientifically study Sb and published his findings in 1707.

The situation with using Sb began to change after the industrial revolution, particularly, over the last 100 years. The primary use of Sb is in industry. For example, very pure Sb is used to make certain types of semiconductor devices, such as diodes and infrared detectors. Sb alloys are used in lead-acid batteries, low friction metals, type metal, cable coverings, microelectronics, solders, bullets and bearings, and in pewter (an alloy of tin, copper and Sb). Other uses of Sb compounds include as a pigment in paints, textiles and glass industries, as well as in the production of the thermoplastic polymer polyethylene terephthalate. Sb compounds is also used in the manufacture of flame-retardant or flame-proofing materials (rubber, plastics, pigments, adhesives, textiles, and paper), as well as in production of some medications and antiprotozoal veterinary drugs [67,70.75].

Thus, inorganic Sb is ubiquitously distributed in environment and food, water, and air everywhere contain this element. In addition to the abundant natural sources of Sb, there are a large number of industrial sources of Sb to the soil (through atmospheric emissions originating from residues from coal, oil, and gas combustion, urban refuse, Au, Cu, Pb, Sb, and Zn mine tailings, smelter slag, waste, including pharmaceutical waste), water (through irrigation and industrial liquid waste, livestock dips, and wastewater sludge application), and air (Sb may be released from metal smelters and from combustion of fossil fuels) contamination. For example, in 1979 year the anthropogenic emission of Sb was estimated as 38,000 tons annually [76]. From the polluted environment Sb is subsequently introduced into the food chain [77]. However, the major source of human exposure to Sb on unpolluted territories is naturally contaminated drinking water [66-68,70].

Sb is an important product in the world economy. Most of the Sb mined today comes from China, which supplies approximately 90% of the world's total. In the end of past century Sb annual production was about 50.000 tons per year but in 2015, the total global volume of Sb production was already approximately 175,500 metric tons. Some Sb is produced as a by-product of smelting ores of metals, mainly gold, copper and silver, in countries such as the United States, Canada, and Australia. Since the use of Sb 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.

As mentioned above, an ingestion of Sb by humans can cause a variety of disorders, such as irritation of the eyes, severe vomiting, diarrhea, skin lesions, lung diseases, heart problems, stomach ulcers [67,70] and different types of cancers, including PCa [31-34]. In spite of a significant correlations between Sb exposure and the risk of PCa have been

reported [31-34], precise molecular mechanisms by which this metalloid causes healthy cells to transform to malignant states have yet to be fully defined. Possibly, production of active oxygen species and/or DNA repair inhibition are mechanisms involved [30].

Thus, according our study for unpolluted areas there are no information could explain the variability of published means for "normal" prostatic Sb levels from 0.0066 mg/kg to 0.071 mg/kg of wet tissue. Moreover, prostate tissue Sb 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 Sb levels. This conclusion was supported the fact that the Certified Reference Materials for quality control of results were not used in old 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 7 to 65), and a total of 1173 "normal" prostates were investigated from all 23 studies. As such, it is hard to draw definite conclusions about the reference value of the Sb content in "normal" prostate as well as about the clinical value of the Sb levels in "normal" prostates as a biomarker.

Conclusion

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

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