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A Systematic Review of the Mercury 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 mercury (Hg) 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 Hg content in the prostatic tissue of healthy subjects.*

***Materials and Methods**: The present study evaluated by systematic analysis the published data for Hg content analyzed in prostatic tissue of "normal" glands. This evaluation reviewed 1978 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 Hg content in prostates of apparently healthy men..*

***Results**: The objective analysis was performed on data from the 22 studies, which included 1194 subjects. It was found that the range of means of prostatic Hg content reported in the literature for "normal" gland varies widely from 0.0043 mg/kg to 0.11 mg/kg with median of means 0.0075 mg/kg on a wet mass basis and the level of intra-prostatic metal increases with age in adults.*

***Conclusion**: Because of small sample size and high data heterogeneity, we recommend other primary studies be performed.*

Keywords: *Mercury; Human prostate; Normal prostatic tissue; Trace elements: 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, including mercury (Hg), can play a significant role in etiology of PCa [16-20]. Moreover, it was demonstrated that the changes of some TE levels and Zn/Hg ratios in prostate tissue can be used as biomarkers [21-27].

Hg has a reputation for being a dangerous element and in past time many people who worked with mercury, for example, miners, mirror makers, hatters, dentists, medical doctors, scientist, and so on, had a lot of problems with their health. Although elemental Hg was clearly toxic, this did not stop its use in pharmacy for hundreds of years. So, the investigations on Hg toxicity have a long story but an intensive study of

problem started after an epidemic in Minamata City in Kumamoto prefecture, Japan in 1956 in which a large number of people died [28].

Among papers reviewed in present study the first result of Hg content in human prostate was published in 1967 [29]. It was indicated that mean level of Hg in human prostates of five adults was 0.11 mg/kg of wet tissue [29]. This finding allowed made the inference that the prostate gland accumulates Hg, because the level of metal in prostate was two orders of magnitude higher the blood serum reference concentration (0.001 mg/L) [30]. Metallic Hg and inorganic compounds of this metal are classified as Group 3 (i.e. 'not classifiable as carcinogenic to humans') by the International Agency for Research on Cancer [31] However, a few epidemiological studies have reported increased cancer incidence (central nervous system, lung, liver, renal and gastric cancer) or mortality associated with occupations involving potential exposure to elemental Hg vapour among workers in chloralkali plants and the nuclear weapon industry, as well as dental professionals [32-37]. Moreover, it was found that higher blood Hg level were associated with a higher prevalence of prostate malignant tumors and nonmelanoma skin cancer [38,39]. These findings promoted more detailed studies of the Hg 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 Hg, 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 [40-42]. In this context, significant Hg exposure may result in adverse health effects in different organs or tissues, including malignancy [32-39,43]. However, precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states are not well understood, but there are some plausible hypotheses: oxidative stress and disruption of DNA repair [39].

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

The present study addresses the significance of Hg 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 Hg 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 August 2020, using the key words: prostatic trace elements, prostatic Hg content, prostatic tissue, and their combinations. For example, the search terms for Hg content were: "Hg mass fraction", "Hg content", "Hg level", "prostatic tissue Hg" and "Hg 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 Hg 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 Hg levels were measured in samples of prostatic tissue.

Exclusion criteria: Studies were excluded if they were case reports. Studies involving subjects that were Hg occupational exposed, as well as persons from Hg 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 Hg determination, number and ages of healthy persons, sample preparation, mean and median of Hg levels, standard deviations of mean, and range of Hg 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 Hg levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of Hg contents. The objective analysis was performed on data from the 22 studies, with 1194 subjects.

Results

Information about Hg 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 [27,38]. Thus, it dictates a need for reliable values of the Hg 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 1978 publications were primarily obtained, of which 1956 irrelevant papers were excluded. Thus, 22 studies were ultimately selected according to eligibility criteria that investigated Hg levels in tissue of normal prostates (Table 1) and these 22 papers [7,9,11,13,14,24,26,29,44-57] comprised the material on which the review was based. A number of values for Hg 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% [58-61] and ash – 1% (on a wet mass basis) contents in normal prostates of adult men [60,62-64].

Table 1 summarizes general data from the 22 studies. The retrieved studies involved 1194 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. Three studies determined Hg levels by destructive (require high temperature drying and acid digestion) analytical methods (Table 1): one - inductively coupled plasma mass spectrometry (ICPMS) and two – radiochemical neutron activation analysis (RNAA). Seven studies detected Hg level in intact prostatic tissue samples by nondestructive analytical method, such as instrumental neutron activation analysis (INAA). In twelve studies a combination of destructive and nondestructive methods (ICPMS and INAA) was used and results were summarized.

Figure 1 illustrates the data set of Hg measurements in 22 studies during the period from 1956 to 2020..

Discussion

The range of means of Hg mass fractions reported in the literature for "normal" prostatic tissue varies widely from 0.0043 mg/kg [7] to 0.11 mg/kg [29] with median of means 0.0075 mg/kg of wet tissue and Mmax/Mmin ratio approximately 26 (Table 1). This variability of reported mean values can be explained a priori by a dependence of Hg content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, possible non-homogeneous distribution of Hg 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 "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 Hg content was measured in pieces of the prostate. Therefore published data allowed us to estimate the effect of only some factors on Hg content in "normal" prostate tissue.

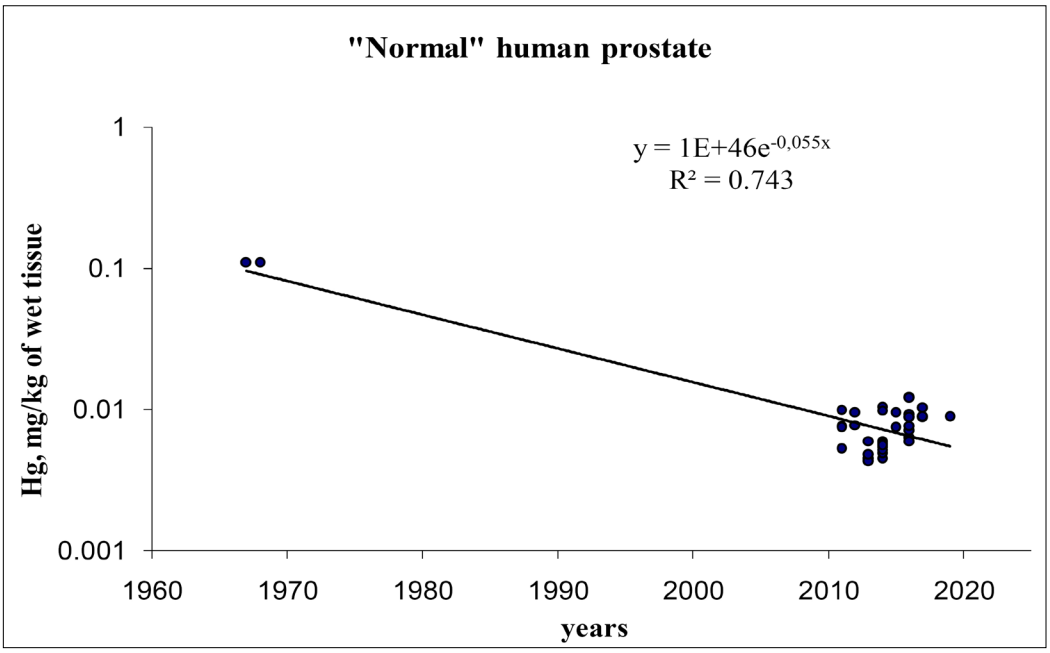

Figure1. *Data on Hg content in normal prostate tissue reported from 1967 to 2020.*

Analytical Method

The trend line of Hg content data in "normal" prostate (Figure 1) showed that an improvement of analytical technologies during last 50 years impacted significantly on the mean of reported values. In our opinion, the leading cause of differences between results published in 1960s and 2010s is a lack of quality control of results with using Certified Reference Materials (CRMs) in old studies.

In some reported papers such destructive analytical methods as RNAA and ICP-MS 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 [40,65,66]. On the other hand, the Hg 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.

Table1. *Reference data of Hg mass fractions (mg/kg wet tissue) in "normal" human prostatic tissue*

Reference	Method	n	Age range years	Sample preparation	Hg	
					M±SD	Range
Smith 1967 [29]	RNAA	5	Adult	D, AD	0.11	0.0068-0.26
Liebscher et al., 1968 [44]	RNAA	5	Adult	D, AD	0.11±0.10	0.0068-0.26
Zaichick et al., 2011 [45]	INAA	64	13-60	Intact	0.0077±0.0078	0.001-0.041
		9	13-20	Intact	0.0075±0.0097	-
		28	21-40	Intact	0.0053±0.0034	-
		27	41-60	Intact	0.010±0.011	-
Zaichick et al., 2012 [24]	INAA	37	66±8	Intact	0.0095±0.0097	0.0013-0.041
Zaichick et al., 2012 [46]	ICPMS	64	13-60	AD	0.0078±0.0075	0.0011-0.045
Zaichick et al., 2013 [7]	INAA	29	0-13	Intact	0.0045±0.0032	-
		21	14-30	Intact	0.0043±0.0022	-
Zaichick et al., 2013 [9]	2 Methods	29	0-13	Intact, AD	0.0060±0.0061	-

		21	14-30	Intact, AD	0.0048±0.0024	-
Zaichick et al., 2014 [47]	INAA	28	21-40	Intact	0.0054±0.0034	0.0014-0.0170
		27	41-60	Intact	0.0104±0.0102	0.0013-0.041
		10	61-87	Intact	0.0045±0.0015	0.0036-0.0067
Zaichick et al., 2014 [48]	2 Methods	28	21-40	Intact, AD	0.0060±0.0037	0.0022-0.0170
		27	41-60	Intact, AD	0.0099±0.0075	0.0013-0.0250
		10	61-87	Intact, AD	0.0063±0.0061	0.0034-0.0221
Zaichick et al., 2014 [11]	INAA	29	0-13	Intact	0.0056±0.0040	
		21	14-30	Intact	0.0049±0.0024	
		50	0-30	Intact	0.0052±0.0033	
Zaichick et al., 2014 [13]	2 Methods	16	20-30	Intact, AD	0.0049±0.0024	-
Zaichick et al., 2014 [14]	2 Methods	50	0-30	Intact, AD	0.0057±0.0033	
		29	0-13	Intact, AD	0.0058±0.0041	
		21	14-30	Intact, AD	0.0056±0.0025	
Zaichick et al., 2015 [49]	INAA	32	44-87	Intact	0.0095±0.0102	0.0013-0.041
Zaichick 2015 [50]	2 Methods	65	21-87	Intact, AD	0.0075±0.0061	-
Zaichick et al., 2016 [51]	INAA	28	21-40	Intact	0.0063±0.0043	0.0019-0.0214
		27	41-60	Intact	0.0122±0.0114	0.0014-0.0480
		10	61=87	Intact	0.0060±0.0019	0.0045-0.0086
Zaichick et al., 2016 [52]	2 Methods	65	21-87	Intact, AD	0.0092±0.0074	0.0015-0.0352
		28	21-40	Intact, AD	0.0071±0.0009	-
		27	41-60	Intact, AD	0.0121±0.0020	-
		10	61=87	Intact, AD	0.0077±0.0023	-
Zaichick et al., 2016 [53]	2 Methods	32	44-87	Intact, AD	0.0088±0.0077	-
Zaichick et al., 2016 [54]	2 Methods	37	41-87	Intact, AD	0.0088±0.0082	-
Zaichick et al., 2017 [26]	2 Methods	37	41-87	Intact, AD	0.0088±0.0082	-
Zaichick et al., 2017 [55]	2 Methods	37	41-87	Intact, AD	0.0103±0.0084	0/0014-0.0335
Zaichick, 2017 [56]	2 Methods	37	41-87	Intact, AD	0.0089±0.0072	0.0013-0.0250
Zaichick et al., 2019 [57]	2 Methods	37	41-87	Intact, AD	0.0089±0.0072	0.0013-0.0250
Median of means		0.0075				
Range of means (M_{min} - M_{max}),		0.0043 – 0.11				
Ratio M_{max}/M_{min}		25.6				
All references		22				

M – arithmetic mean, SD – standard deviation of mean,

RNAA – radiochemical neutron activation analysis, NAA – instrumental neutron activation analysis, ICPMS – inductively coupled plasma mass spectrometry; 2 Methods –NAA and ICPMS, D – drying at high temperature, AD – acid digestion.

It is possible to avoid these problems by using non-destructive methods, such as INAA, which allow quantify Hg content in "normal" prostate without acid digestion. Moreover, a good agreement between results obtained by both INAA and ICPMS methods under a strong quality control with using CRMs [9,13,14,26,52-54,55-57] shoved that in case of Hg 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 Hg content in prostatic tissue as biomarkers.

Age

In a few studies a significant increase in Hg content with increasing of age of adults was shown by the comparison of different age groups or the Pearson's coefficient of correlation between age and Hg content in prostate tissue [47,48,50-52]. For example, a strongly pronounced tendency for an age-related increase of Hg mass fraction was observed in the prostate for the third to six decades [50]. In prostates of 50 year old men, the mean Hg mass fraction was 2-3 times greater than that in the prostates of 20 year old males [50]. Thus, the accumulated information, studied by us from reported data, allowed a conclusion that there is a significant increase in Hg mass fraction in "normal" prostate from age 21 years to the six decade.

Androgen-Independence of Prostatic Hg levels

There was not found any difference between Hg levels in prostates of teenagers before puberty and of postpubertal teenagers and young adults [7,9,11,13,14]. These findings allowed us to conclude that the Hg content in "normal" prostates does not depend on the level of androgens, and vice versa. However, studies on the association between the Hg content in "normal" prostates and the level of androgens in blood were not found.

Hg Intake

In the general population, potential sources of Hg exposure include the inhalation of this metal vapor in the air, ingestion of contaminated foods and drinking water, and exposure to dental amalgam through dental care [67]. Fish, shellfish and marine products consumption is one of the major route of human exposure to Hg [43]. Recent studies indicate that rice consumption could also contribute significantly to human exposure to Hg, but especially in Asia [68]. A strong positive association between alcohol consumption and blood Hg levels was also reported [67]. The Joint Food and Agriculture Organization of the United Nations and World Health Organization FAO/WHO Expert Committee on Food Additives (JECFA) has established provisional tolerable weekly intake (PTWI) for total Hg, The PTWI for Hg of 4.0 μg/kg body weight/week corresponds to 0.280 mg/ week for a person weighing 70 kg [69]. Other general population exposures may result from dental fillings (dental amalgam is made up of approximately 40-50% Hg, 25% Ag, and 25-35% blend of Cu, Zn and Sn) and using or breaking products containing Hg such as some thermometers, barometers, novelty jewelry and etc [37,69].

Hg Content in Body Fluids, Tissues and Organs

It is known that Hg is deposited primarily in the brain, lung, liver, kidney, adrenals, pancreas, muscles including myocardium, thyroid, breast, prostate, testes, enterocytes, skin, sweat and salivary glands [69]. Mass fraction of this metal in blood serum of the Reference Man is lower 0.001 mg/L [30]. The median of prostatic Hg content means obtained in the present review (0.0075 mg/kgof wet tissue) is almost one order of magnitude higher the blood serum value. Thus, we can confirm that the prostate is a target organ for Hg. An increase of Hg intake associated with an increase of metal concentration in blood [67,70], and, as a consequence in different organs, including the prostate.

All natural chemical elements of the Periodic System, including Hg, present in all subjects of biosphere [41,71,72]. During the long evolutional period intakes of Hg were more or less stable and organisms were adopted for such environmental conditions. People use metallic Hg in very small amounts for a long time. Mercury has been found in Egyptian tombs dating to about 1500 B.C., and it was probably used for cosmetic and medicinal purposes even earlier.

The situation very changed after the industrial revolution, particularly, after 1900 when Hg found its way into many products and industrial applications. Principal applications of Hg are in the production of chlorine and caustic soda. Other uses for metallic Hg and Hg compounds include production of light bulbs, light switches, electrical equipment, batteries, semi-conductors, instrument engineering (barometers and thermometers), explosives, jewelries, paints, sporting equipment, fungicides, and pesticides. Hg is also used as part of the processes to produce car, paper, felt, leather, glass, and many plastics, as well as as a preservative or antibacterial agent in medical and pharmaceutical applications (antibiotics, blood pressure cuffs, contact

lens solution, dental amalgam, diuretics, ear and eye drops, eye ointment, hemorrhoid relief ointment, nasal spray, and medical thermometers).

Environmental Hg pollution occurs mainly through a combination of land (through atmospheric emissions originating from mining and refining, various manufacturing operations, residues from coal, oil, and gas combustion, urban refuse, and also from waste, fungicides, pesticides, and sewage sludge application), water (through irrigation, industrial liquid waste, and sewage sludge), and air (through atmospheric industrial emissions and vehicle exhaust) contamination and is subsequently introduced into the food chain. Worldwide, in 1988 approximately 11 t of Hg were released into the air, land, and water as the result of human activities. In 2000s global direct emissions to the atmosphere amounted to 30 t per year and the total quantity of Hg released into the air during the past five centuries exceeded 10000 t [73]. Thus, the global demand for Hg and global environmental contamination by this metal increased till now. Moreover, it is likely that this tendency will continue. Age-dependent increase of Hg mass fractions in the 'normal" prostate tissue indirectly confirm this conclusion. If an increase of Hg in prostate of healthy men living in a non-industrial, ecologically safe region will be confirmed, this could be interpreted as the result of a global increase of the concentrations of Hg in the environment.

Thus, according our study for not polluted areas no one influencing factor could explain the variability of published means for prostatic Hg levels from 0.0043 mg/kg to 0.11 mg/kg of wet tissue. Moreover, prostate tissue Hg contents showed large variations among individuals, but sources of the variation remain unknown. For example, the most powerful factor was age when it was found that the prostatic Hg level of young adults was only 2-3 times lower than that of men aged 50-60 years. 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 Hg levels. This conclusion was supported the fact that the Certified Reference Materials for quality control of results were not used in studies reported in 1960s [29, 44].

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 65), and a total of 1194 "normal" controls were investigated from all 22 studies. As such, it is hard to draw definite conclusions about the reference value of the Hg content in "normal" prostate as well as about the clinical value of the Hg levels in "normal" prostates as a biomarker.

Conclusion

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

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