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Review article

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A Systematic Review of the Aluminum 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 aluminum (Al) 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 Al content in the prostatic tissue of healthy subjects. The present study evaluated by systematic analysis the published data for Al content analyzed in prostatic tissue of "normal" glands. This evaluation reviewed 1981 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 Al content in prostates of apparently healthy men. The objective analysis was performed on data from the 25 studies, which included 1190 subjects. It was found that the range of means of prostatic Al content reported in the literature for "normal" gland varies widely from 0.89 mg/kg to mg/kg with median of means 29.0 mg/kg on a wet mass basis. Finally, because of small sample size and high data heterogeneity, we recommend other primary studies be performed.

Keywords: Aluminum, 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 aluminum (Al), and Zn/TE content ratios in prostate tissue, including Zn/Al ratio, can be used as biomarkers [20-26].

The effects of TEs, including Al, 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 [27-29]. In this context, low-level Al exposure has been strongly correlated with carcinogenesis in the breast tissue [30-31]. Furthermore, elevated Al content has been found in the malignant tumors of many organs, including prostate gland [25,32-35]. Thus, a role for this common environmental contaminant in human PCa initiation and/or progression would be very important.

By now, an exceedingly scant literature exists on quantitative Al 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 Al 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 Al 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 Al content, prostatic tissue, and their combinations. For example, the search terms for Al content were: "Al mass fraction", "Al content", "Al level", "prostatic tissue Al" and "Al 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 Al 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 Al levels were measured in samples of prostatic tissue.

Exclusion criteria

Studies were excluded if they were case reports. Studies involving persons from Al contaminated area and subjects that were Al 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 Al determination, number and ages of healthy persons, sample preparation, mean and median of Al levels, standard deviations of mean, and range of Al 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 Al levels in prostatic tissue. The articles were analyzed and "Median of Means" and "Range of Means" were used to examine heterogeneity of Al contents. The objective analysis was performed on data from the 25 studies, with 1190 subjects.

Results

Information about Al 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 [32-36]. Thus, it dictates a need for reliable values of the Al 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 1981 publications were primarily obtained, of which 1956 irrelevant papers were excluded. Thus, 25 studies were ultimately selected according to eligibility criteria that investigated Al levels in tissue of "normal" prostates (Table 1) and these 25 papers comprised the material on which the review was based [8,9,12-14,25,32-50]. A number of values for Al 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% and ash – 1% (on a wet mass basis) contents in "normal" prostates of adult men [39,51-56].

Table 1 summarizes general data from the 25 studies. The retrieved studies involved 1190 subjects. The ages of subjects were available for 21 studies and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 24 studies. Five studies determined Al levels by destructive (require high temperature drying, ashing, and acid digestion,) analytical methods (Table 1): one using inductively coupled plasma atomic emission spectrometry (ICPAES), one - inductively coupled plasma mass spectrometry (ICPMS), and three – atomic emission spectrometry (AES). In nineteen studies a combination of destructive (ICPAES and ICPMS) methods and nondestructive neutron activation analysis (NAA) was used and results were summarized.

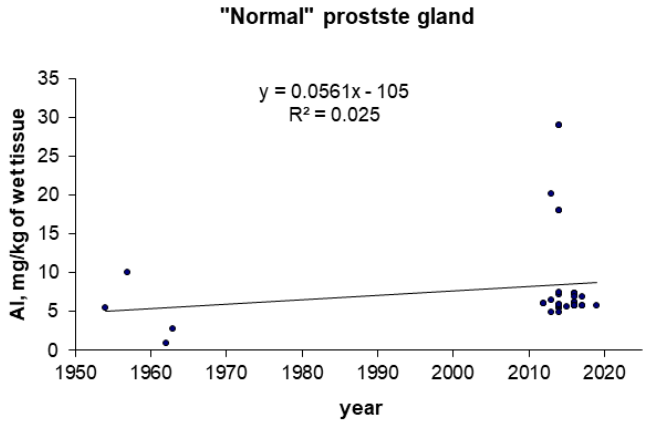

Figure 1: illustrates the data set of Al measurements in 25 studies during the period from 1960 to 2020.

Discussion

The range of means of Al mass fractions reported in the literature for "normal" prostatic tissue varies widely from 0.89 mg/kg to 29 mg/kg with median of means 5.95 mg/kg wet tissue (Table 1) [12,38]. The maximal value of mean Al mass fraction reported was 32.6 times higher the minimal value (Table 1) [12]. This variability of reported mean values can be explained by a dependence of Al content on many factors, including analytical method imperfections, differences in "normal" prostate definitions, possible non-homogeneous distribution of Al 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). In some studies

whole glands were used for the investigation while in others the Al content was measured in pieces of the prostate. Therefore published data allowed us to estimate the effect of only some factors on Al content in "normal" prostate tissue.

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

Reference	Method	n	Age, years M(Range)	Sample preparation	Al	
					M±SD	Range
Tipton et al. 1954 [36]	AES	8	Adult	D, A	5.53	-
Stitch 1957 [37]	AES	9	Adult	D, A	10	-
Zakutinsky et al. 1962 [38]	-	-	Adult	-	0.89	-
Tipton et al. 1963 [39]	AES	50	Adult	D, A	2.7±14.0	-
Zaichick et al. 2012 [40]	ICP-AES	64	13-60	AD	6.09±3.94	1.16-20.6
Zaichick et al. 2012 [41]	ICP-MS	64	13-60	AD	6.09±3.94	1.16-20.6
Zaichick et al. 2013 [8]	NAA+ICPAES	16	20-30	Intact, AD	4.93±2.89	-
Zaichick et al. 2013 [9]	NAA+ICPMS	29	0-13	Intact, AD	20.2±20.9	-
		21	14-30	Intact, AD	6.43±4.85	-
Zaichick et al. 2014 [12]	NAA+ICPAES	50	0-30	Intact, AD	18±27	-
		29	0-13	Intact, AD	29±35	-
		21	14-30	Intact, AD	7.2±5.8	-
Zaichick et al. 2014[13]	NAA+ICPMS	50	0-30	Intact, AD	18±27	-
		29	0-13	Intact, AD	29±35	-
		21	14-30	Intact, AD	7.4±6.0	-
Zaichick et al. 2014 [14]	3 Methods	16	20-30	Intact, AD	4.93±2.89	-
Zaichick et al. 2014 [42]	NAA+ICPAES	28	21-40	Intact, AD	5.44±3.23	1.16-11.6
		27	41-60	Intact, AD	5.78±3.23	1.63-12.5
		10	61-87	Intact, AD	5.95±2.72	2.64-10.5
Zaichick et al. 2014 [43]	NAA+ICPMS	28	21-40	Intact, AD	5.44±3.16	1.16-11.6
		27	41-60	Intact, AD	5.76±3.20	1.63-12.5
		10	61-87	Intact, AD	5.90±2.72	2.64-10.5
Zaichick 2015 [44]	3 Methods	65	21-87	Intact, AD	5.61±3.06	-
Zaichick et al. 2016 [45]	NAA+ICPAES	28	21-40	Intact, AD	6.21±0.90	-
		27	41-60	Intact, AD	7.34±1.02	-
		10	61-87	Intact, AD	7.30±1.4	-
Zaichick et al. 2016 [46]	NAA+ICPMS	28	21-40	Intact, AD	6.21±4.76	-
		27	41-60	Intact, AD	7.34±5.30	-
		10	61-87	Intact, AD	7.30±4.43	-
		65	21-87	Intact, AD	6.88±3.95	1.61-17.3
Zaichick et al. 2016 [32]	NAA+ICPAES	37	41-87	Intact, AD	5.78±3.06	1.63-12.5
Zaichick et al. 2016 [47]	NAA+ICPAES	32	44-87	Intact, AD	5.78±3.06	1.63-12.5
Zaichick et al. 2016 [33]	NAA+ICPAES	37	41-87	Intact, AD	5.80±3.01	1.63-12.5
Zaichick et al. 2016 [48]	NAA+ICPMS	32	44-87	Intact, AD	5.81±3.55	-
Zaichick et al. 2016 [34]	NAA+ICPMS	37	41-87	Intact, AD	5.81±3.62	-
Zaichick et al. 2017 [25]	NAA+ICPMS	37	41-87	Intact, AD	5.81±3.62	-
Zaichick et al. 2017 [49]	3 Methods	37	41-87	Intact, AD	6.95±1.69	1.70-16.5
Zaichick 2017 [35]	3 Methods	37	41-87	Intact, AD	5.80±3.01	1.63-12.5
Zaichick et al. 2019 [50]	3 Methods	37	41-87	Intact, AD	5.80±3.01	1.63-12.5

Median of means	5.95
Range of means (M_{min} - M_{max}),	0.89 – 29.0
Ratio M_{max}/M_{min}	32.6
All references	25

M – arithmetic mean, SD – standard deviation of mean, AES – atomic emission spectrometry, ICPAES – inductively coupled plasma atomic emission spectrometry, ICPMS – inductively coupled plasma mass spectrometry, NAA – neutron activation analysis, 3 Methods – NAA+ICPAES+ICPMS D – drying at high temperature, A – ashing, AD – acid digestion.

Analytical method

The trend line of Al content data in "normal" prostate (Figure 1) showed that an improvement of analytical technologies during last 66 years did not impact significantly on the mean of reported values. In our opinion, the leading cause of inter-observer Al content variability was insufficient quality control of results in published studies. Almost in all reported papers such destructive analytical methods as AES, ICPAES, 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 [27,57,58]. On the other hand, the Al 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 quantify Al content in "normal" prostate without acid digestion. Moreover, a good agreement between results obtained by both INAA and ICPAES/ICPMS methods under a strong quality control with using CRMs shoved that in case of Al it is possible to avoid uncertainties connected with acid digestion [8,9,12-14,25,32-35,42-50]. It is, therefore, reasonable to conclude that the quality control of results is very important factor for using the Al content in prostatic tissue as biomarkers.

Age

In a few studies an elevated level of Al content was found in prostates of children [9,12,13]. However, neither the comparison of different age groups nor using the Pearson's correlation between age and Al content in prostate tissue of adults indicated any age-related changes during 21 to 87 years [42,43,45,46].

Androgen-independence of prostatic Al level

There was not found an increase of Al levels in prostates of teenagers after puberty [9,12,13]. These findings allowed us to conclude that the Al content in "normal" prostates does not associate with the level of androgens in blood.

Al content in body fluids, tissues and organs

It is known that Al is accumulated primarily in liver, kidney cortex, brain, lung, and bones [59,60]. For example, mass fraction of this metal in the liver of Reference Man ranged from 0.0003 to 0.002 mg/kg of wet tissue [61]. The median of prostatic Al content means obtained in the present review (5.95 mg/kg of wet tissue) is almost three orders of magnitude higher the metal level in liver. Thus, we can conclude that the prostate is a target organ for Al and a small increase of Al concentration in blood for a long period may associate with a great increase of this metal in different target organs, including the prostate.

Al is the most abundant chemical element on Earth behind oxygen and silicon, making it the most abundant metal naturally found on the planet. All natural chemical elements of the Periodic System, including Al, present in all subjects of biosphere [27,62,63]. During the long evolutional period intakes of Al 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 [64]. The situation began to change after the industrial revolution, particularly, over the last 100 years.

In spite of a pure form of the Al was first successfully extracted from ore in 1825, techniques to produce aluminum in ways modestly cost-effective emerged only in 1889. Before this date humans never contact with Al as a pure metal. Now Al is the second-most used metal globally, behind only iron and it is largely used as an alloy. The primary use of Al is in industry, for example, in power lines, high-rise buildings, window frames, consumer electronics, aircraft and spacecraft components, ships, trains, personal vehicles, household appliances, and many others. Al compounds are also used in cosmetics (antiperspirants, sun creams, toothpaste) and medicine (in vaccines to elicit a more powerful immune response and in desensitization procedures [30,31,65]. Al powders are used in pigments and paints, fuel additives, explosives and propellants. Al oxides are used as food additives and in the manufacture of, for example, abrasives, refractories, ceramics, electrical insulators, catalysts, paper, spark plugs, light bulbs, artificial gems, alloys, glass and heat resistant fibres. Food related uses of Al compounds include preservatives, fillers, coloring agents, anti-caking agents, emulsifiers and baking powders. Natural Al minerals especially bentonite and zeolite are used in water purification, sugar refining, brewing and paper industries [66].

Thus, Al is a unique metal with numerous pathways of exposure and food, water, and air everywhere contain this element. In addition to the abundant natural sources of Al, such as forest fires, volcanoes and other geothermal sources and emissions from land and water, there are a large number of industrial sources of metal to the soil, water, and air contamination [67]. From the global polluted environment Al is subsequently introduced into the food chain. In absence of occupational exposures and chronic use of Al-containing antacids and buffered aspirin, food is the major intake source of Al, followed by drinking water [66]. The additional sources of human exposure to Al are Al-containing food packaging, foils, cooking utensils and baking trays made of Al, cosmetic products (antiperspirants, sun creams, toothpaste) and drugs (antacid agents) [65,68].

In 2004, Al was being produced in 41 countries, the largest producers being China, Russia, Canada and the United States [66].

Now the global annual production of Al is 417712 thousand metric tons, with China contributing to the maximum proportion followed by the Gulf Co-operation Council, North America, and India [69]. Globally, auto and transport account for 23% of Al consumption, followed by construction (22%), packaging (13%), electrical (12%), machinery and equipment (8.5%), consumer durables (4.5%), and other segments (4%). To meet the increasing demand for Al, there is a continuous rise in its production, which is projected to increase 2.5 times from 2014 to 2050 [69]. All of this Al has the potential, at least, to enter and accumulate within the biotic cycle [70]. Thus, we can conclude that the human body burden of Al, including prostate tissue, has increased over the last 100 years due to an increase in global environmental Al pollution and, as a consequence, in dietary exposure to this metal [71]. It is likely that this tendency will continue.

Following oral exposure, Al distributes throughout the organism with accumulation in bone, kidneys, liver, and brain being of concern to humans with evidence of renal dysfunction, anemia or neurobehavioural alterations reported after excessive doses [66]. It is clear that high levels of Al in central nervous system can lead to neurotoxicity and play a role in etiology of Alzheimer's Disease. There is clear evidence that sustained exposure to high levels of Al can cause bone abnormalities, because this metal is clearly deposited in bone at sites of new growth. Furthermore, Al overload leads to parathyroid hormone suppression and with regards to the bone, may be associated with altered calcium homeostasis [66].

Because Al exposure was strongly correlated with carcinogenesis in the lung and breast tissues, "Al production" was classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC) [66]. Elevated Al content was found in the tumorous tissues of persons with breast, colorectal, bladder, and PCa [30-35,65,72]. However, precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states have yet to be fully defined. Al is known to have a genotoxic profile, capable of causing both DNA alterations and epigenetic effects [30]. Al compounds were associated with oxidative stress, DNA double strand breaks, and uncontrolled cell growth [31]. Al was observed to act as a metalloestrogen, which behaves as an agonist for estrogen receptors. This adds Al to the increasing list of metals capable of interfering with oestrogen action (metalloestrogens) and to disturb sex-hormones balance [30].

Thus, according our study for unpolluted areas there are no information could explain the variability of published means for "normal" prostatic Al levels from 0.89 mg/kg to 29.0 mg/kg in wet tissue. Moreover, prostate tissue Al 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 Al 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 8 to 65), and a total of 1190 "normal" prostates were investigated from all 25 studies. As such, it is hard to draw definite conclusions about the reference value of the Al content in "normal" prostate as well as about the clinical value of the Al levels in "normal" prostates as a biomarker.

Conclusion

The present study is a comprehensive study regarding the determination of Al content in "normal" human prostates. With this knowledge Al levels may then be considered as a biomarker for the recognition of prostate disorders. The study has demonstrated that levels of Al 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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