

A Systematic Review of the Lead Content of the Normal Human Prostate Gland

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Review Article

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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 lead (Pb) 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 Pb content in the prostatic tissue of healthy subjects. The present study evaluated by systematic analysis the published data for Pb content analyzed in prostatic tissue of "normal" glands. This evaluation reviewed 1997 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 Pb content in prostates of apparently healthy men. The objective analysis was performed on data from the 26 studies, which included 998 subjects. It was found that the range of means of prostatic Pb content reported in the literature for "normal" gland varies widely from 0.026 mg/kg to 1.6 mg/kg with median of means 0.275 mg/kg on a wet mass basis. The Pb content depends on many factors such as analytical method, age, dietary Pb intake, and smoking. Finally, because of small sample size and high data heterogeneity, we recommend other primary studies be performed.

Keywords: Lead; 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, including lead (Pb), can play a significant role in etiology of PCa [16-20]. Moreover, it was demonstrated that the changes of some TE levels and Zn/Pb ratios in prostate tissue can be used as biomarkers [21-27].

The first finding of Pb in human prostatic tissue was reported in 1954 [28]. Tipton et al. [28] analyzed Pb and other TE contents in

many organs and tissues of human body. They found that mean Pb content in the eight prostates were approximately 0.29 mg/kg of wet prostatic tissue. However, sixteen years later Soman et al. [29] shown that the Pb mass fraction in human prostate (1.6 mg/kg wet tissue) is more than 5 times higher than the result previously published by Tipton et al. [28]. This result allowed conclude that the prostate gland accumulates Pb, because the levels of metal in prostates was almost 5 times higher than in liver (0.30 mg/kg wet tissue) and more than 3 orders of magnitude higher than in blood serum (<0.001 mg/L) of the Reference Man [30]. Furthermore, experimental and epidemiological data identified that Pb compounds should be considered as genotoxic carcinogens [20, 31-33]. Consequently, the International Agency for Research on Cancer (IARC) classified inorganic Pb as a probable carcinogen [31]. These findings promoted more detailed studies of the Pb content of prostatic tissue of healthy and occupationally exposed subjects, as well as in those with different prostatic diseases,

including BPH and PCa.

The effects of TEs, including Pb, 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 [34-36]. In this context, significant correlations between Pb exposure and the risk of human brain, lung, stomach, kidney, breast, and prostate cancer have been reported [20, 31-33, 37, 38]. However, precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states have yet to be fully defined.

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

The present study addresses the significance of Pb 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 Pb 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 Pb content, prostatic tissue, and their combinations. For example, the search terms for Pb content were: “Pb mass fraction”, “Pb content”, “Pb level”, “prostatic tissue Pb” and “Pb 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 Pb 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 Pb levels were measured in samples of prostatic tissue.

Exclusion criteria

Studies were excluded if they were case reports. Studies involving persons from Pb contaminated area and subjects that were Pb 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 Pb determination, number and ages of healthy persons, sample preparation, mean and median of Pb levels, standard deviations of mean, and range of Pb 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 Pb levels in prostatic tissue. The articles were analyzed and “Median of Means” and “Range of Means” were used to examine heterogeneity of Pb contents. The objective analysis was performed on data from the 26 studies, with 998 subjects.

Results

Information about Pb 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 [20, 27]. Thus, it dictates a need for reliable values of the Pb 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 1997 publications were primarily obtained, of which 1971 irrelevant papers were excluded. Thus, 26 studies were ultimately selected according to eligibility criteria that investigated Pb levels in tissue of normal prostates (Table 1) and these 26 papers [9, 13, 14, 26, 28, 29, 39-58] comprised the material on which the review was based. A number of values for Pb 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% [59-62] and ash – 1% (on a wet mass basis) contents in normal prostates of adult men [42, 43, 47, 61].

Table 1 summarizes general data from the 26 studies. The retrieved studies involved 998 subjects. The ages of subjects were available for 14 studies and ranged from 0–89 years. Information about the analytical method and sample preparation used was available for 24 studies. All twenty four studies determined Pb levels by destructive (require high temperature drying, ashing, acid digestion, fixation in ethanol/chloroform/formaldehyde, paraffin/resin embedding, and defatting of tissue samples) analytical methods (Table 1): two using chemical analysis, two - solution absorption spectrometry (SAS), three - atomic absorption spectrophotometry (AAS), four - atomic emission spectrometry (AES), and thirteen - inductively coupled plasma mass spectrometry (ICPMS).

| Reference | Method | n | Age, years M(Range) | Sample preparation | Pb | |
|--------------------------------|----------|----|---------------------|--------------------|-------------|------------|
| | | | | | M±SD | Range |
| Tipton et al. 1954 [28] | AES | 8 | Adult | D, A | 0.29 | - |
| Koch et al. 1956 [39] | AES | 4 | Adult | AD | 0.15 | - |
| ICRP 1960 [40] | - | - | - | - | 0.91 | - |
| Zakutinsky et al. 1962 [41] | - | - | - | - | 0.91 | - |
| Tipton et al. 1963 [42] | AES | 50 | Adult | D, A | 0.10 | Max. 0.27 |
| Schroeder et al. 1968 [43] | AES | 50 | Adult | D, A | 0.10 | - |
| Barry et al. 1970 [44] | SAS | 29 | - | - | 0.32 | - |
| Soman et al. 1970 [29] | AAS | 4 | Adult | A, AD | 1.6 | - |
| Barry 1975 [45] | SAS | 53 | 0-89 | A, AD | 0.27±0.51 | 0.03-2.82 |
| | | 3 | 0-9 | A, AD | 0.35 | 0.1-0.5 |
| | | 6 | 10-19 | A, AD | 0.13 | 0.03-0.25 |
| | | 9 | 20-29 | A, AD | 0.09 | 0.04-0.05 |
| | | 4 | 30-39 | A, AD | 0.08 | 0.05-0.11 |
| | | 8 | 40-49 | A, AD | 0.12 | 0.04-0.23 |
| | | 9 | 50-59 | A, AD | 0.15 | 0.04-0.58 |
| | | 15 | 60-69 | A, AD | 0.46 | 0.03-2.82 |
| | | 3 | 70-79 | A, AD | 0.17 | 0.07-0.33 |
| | | 4 | 80-89 | A, AD | 1.04 | 0.08-2.51 |
| Gross et al. 1975 [46] | Chemical | 46 | Adult | A, AD | 0.20±0.22 | - |
| Saltzman et al. 1990 [47] | Chemical | 57 | 20-84 | A, AD | 0.20±0.21 | - |
| Oldereid et al. 1993 [48] | AAS | 41 | 40(18-80) | FF, AD | 0.026 | - |
| Benoff et al. 2003 [49] | AAS | 6 | Adult | F, AD | 0.177±0.035 | - |
| Zaichick et al. 2012 [50] | ICPMS | 64 | 13-60 | AD | 0.30±0.41 | 0.032-1.82 |
| Zaichick et al. 2013 [9] | ICPMS | 16 | 20-30 | AD | 0.22±0.22 | - |
| Neslund-Dudas et al. 2014 [51] | ICPMS | 21 | Adult NS | F, P, AD, NB | 0.030 | - |
| | | 25 | Adult ES | F, P, AD, NB | 0.046 | - |
| Zaichick et al. 2014 [52] | ICPMS | 28 | 21-40 | AD | 0.19±0.24 | 0.043-0.92 |
| | | 27 | 41-60 | AD | 0.43±0.53 | 0.044-1.82 |
| | | 10 | 61-87 | AD | 0.34±0.37 | 0.026-1.04 |
| Zaichick et al. 2014 [13] | ICPMS | 16 | 20-30 | AD | 0.124±0.168 | - |
| Zaichick et al. 2014 [14] | ICPMS | 50 | 0-30 | AD | 0.28±0.28 | - |
| | | 29 | 0-13 | AD | 0.41±0.30 | - |
| | | 21 | 14-30 | AD | 0.15±0.20 | - |
| Zaichick 2015 [53] | ICPMS | 65 | 21-87 | AD | 0.32±0.43 | - |
| Zaichick et al. 2016 [54] | ICPMS | 32 | 44-87 | AD | 0.42±0.56 | - |
| Zaichick et al. 2016 [55] | ICPMS | 37 | 41-87 | AD | 0.41±0.57 | - |
| Zaichick et al. 2017 [26] | ICPMS | 37 | 41-87 | AD | 0.48±0.57 | 0.028-1.77 |
| Zaichick 2017 [57] | ICPMS | 37 | 41-87 | AD | 0.41±0.49 | 0.026-1.82 |
| Zaichick et al. 2019 [58] | ICPMS | 37 | 41-87 | AD | 0.41±0.49 | 0.026-1.82 |
| Median of means | | | 0.275 | | | |
| Range of means (Mmin - Mmax), | | | 0.026 – 1.60 | | | |
| Ratio Mmax/Mmin | | | 61.5 | | | |
| All references | | | 26 | | | |

Table 1: Reference data of Pb mass fractions (mg/kg wet tissue) in “normal” human prostatic tissue.

M – arithmetic mean, SD – standard deviation of mean, AES – atomic emission spectrometry, SAS – solution absorption spectrometry, AAS – atomic absorption spectrophotometry, ICPMS – inductively coupled plasma mass spectrometry;

NS – never-smokers, ES – ever-smokers, D – drying at high temperature, A – ashing, AD – acid digestion, FF – defatted (fat free), F – fixed in ethanol/chloroform/formaldehyde, P – paraffin embedded, NB – needle biopsy.

Figure 1 illustrates the data set of Pb measurements in 26 studies during the period from 1954 to 2020.

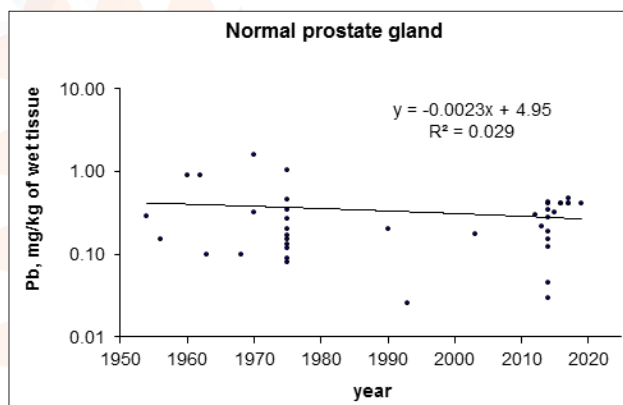


Figure 1: Data on Pb content in normal prostate tissue reported from 1954 to 2020 year

Discussion

The range of means of Pb mass fractions reported in the literature for “normal” prostatic tissue varies widely from 0.026 mg/kg [48] to 1.60 mg/kg [29] with median of means 0.275 mg/kg wet tissue (Table 1). Thus, the maximal value of mean Pb mass fraction reported [29] was 61.5 times higher the minimal value of mean [48]. This variability of reported mean values can be explained by a dependence of Pb content on many factors, including analytical method imperfections, differences in “normal” prostate definitions, possible non-homogeneous distribution of Pb 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. 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 Pb content was measured in pieces of the prostate. Therefore published data allowed us to estimate the effect of only a few factors on Pb content in “normal” prostate tissue.

Analytical method

The trend line of Pb content data in “normal” prostate (Figure 1) showed that an improvement of analytical technologies during last

66 years did not impact significantly on the means and variability of reported values. Thus, in our opinion, the leading cause of inter-observer variability was insufficient quality control of results in published studies. In all reported papers destructive analytical methods were used. These methods require drying, ashing or 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 [34, 63, 64]. On the other hand, the Pb 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 Pb, 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 quantify Pb 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 Pb content in prostatic tissue as biomarkers.

Age

In a few studies a significant increase in Pb content with increasing of age was shown by the comparison of different age groups or the Pearson’s coefficient of correlation between age and Pb content in prostate tissue [14, 45, 52]. The most detailed investigations of age-dependence of prostatic Pb were done by Barry et al. [45]. For example, a strongly pronounced tendency for an age-related increase of Pb mass fraction was observed in the prostate for the third to nine decades [45]. In prostates of 60-89 year old men, the mean Pb mass fraction was 6 times greater than that in the prostates of 20-39 year old males. Thus, the accumulated information, studied by us from reported data, allowed a conclusion that there is a significant increase in Pb mass fraction in “normal” prostate from age 21 years to the sixth-nine decades.

Androgen-independence of prostatic Pb levels

There was not found any difference between Pb levels in prostates of teenagers before puberty and of postpubertal teenagers and young adults [9, 13, 14, 45]. These findings allowed us to conclude that the Pb content in “normal” prostates does not depend on the level of androgens, and vice versa.

Dietary Pb intake

Pb exposure occurs through various ways like ingestion, inhalation, and skin contact. For nonsmokers, food and drinking water are the main sources of Pb exposure [65, 66]. Most people receive the largest portion of their daily Pb intake via food. Weekly Pb dietary intakes for Europe adults vary widely from 1.7 to 60 µg/kg body weight between different countries [67, 68], however prolonged intake of even this low level of Pb is hazardous to human beings [66]. Pb is contained in all kinds of food. The highest contents of Pb as usual are found in grape juice, fruits (apple and pear), and root vegetables (potatoes and carrots) [65, 66]. It was shown that a strong link exists between Pb intake and this metal level in key organs, such as bones, teeth, liver, and kidney [71]. From this it was hypothesized that dietary Pb intake affects the metal’s levels in the prostate and data for prostatic Pb of smokers and

nonsmokers indirectly support this hypothesis.

Smoking

Smoking is an important source of Pb exposure [69, 70]. Unlike Pb in food, which is poorly absorbed (about 10% in adults), approximately 95% of this metal in inhaled smoke is absorbed into the bloodstream [66]. In the study Neslund-Dudas et al. [51] Cd contents of tumor and adjacent non-neoplastic prostate tissue were measured by ICP-MS. The prostate cancer cases in this study included 21 never-smokers and 25 ever-smokers. Smokers and never-smokers were similar in age, PSA at diagnosis, and Gleason grade. In addition, dietary Zn intake and estimated occupational exposure to metals did not differ between ever- and never-smokers. It was found that current smokers had 1.54 times the Pb level in tumor-adjacent non-neoplastic tissue of never smokers. These findings warrant the conclusion that the Pb contents in “normal” prostates significantly depend on smoking.

Prostatic Pb content in comparison with other body organs, tissues, and fluids

Absorbed Pb is deposited primarily in bone and teeth (from 94 to 99% for adults) [66, 72, 73]. Among soft tissues of human body (blood, liver, kidney, brain etc) the highest Pb concentrations were found for liver and kidney [65, 66]. Mass fraction of this metal in blood serum and liver of the Reference Man is <0.001 mg/L and 0.30 mg/kg of wet tissue, respectively [30]. Because the median of prostatic Pb content means obtained in the present review (0.275 mg/kg of wet tissue) is two order of magnitude higher the blood serum value and comparable to metal content in liver, it is reasonable to confirm that the prostate is a target organ for Pb.

For biokinetic movements of Pb in the body more often used a three-compartment model [74, 75]. Pb within these three compartments, namely blood (the most labile pool), bone (the most stable pool) and soft tissues (labile pool) has different half-times, for example, about 36 days, 27 years, and 40 days, respectively [74, 75]. Anyway, in spite of the possible changes in Pb intake, humans are in a state of positive Pb balance from birth [74, 75]. It means the increase of Pb content in bone and in other key organs, including prostate, with the increase of age (see paragraph “Age”).

All natural chemical elements of the Periodic System, including Pb, present in all subjects of biosphere [34, 76, 77]. During the long evolutionary period intakes of Pb 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 metal in their functions [78] Pb is one of the earliest metals discovered by the human race and environmental conditions began to change in the ancient world when people started to use intensively this metal in their life. For example, lead poisoning is believed to be primarily responsible for the collapse of the Roman Empire and Beethoven’s death [66]. However, a really drastically increase of Pb intake links with the industrial revolution, particularly, over the last 100 years with appearing various sources of this metal exposure like Pb contained gasoline, industrial smelting of Pb and its combustion, pottery, boat building, Pb based painting, Pb containing pipes, battery recycling, grids, arm industry, pigments, printing of books, etc. [65, 66].

Environmental Pb pollution occurs mainly through a combination of land (through atmospheric emissions originating from residues from coal, oil, and gas combustion, urban refuse, mine tailings and smelter slag, and also from waste, fertilisers and sludge application), water (through irrigation and industrial liquid waste), and air (through atmospheric industrial emissions and vehicle exhaust) contamination and is subsequently introduced into the food chain. Pb important properties like softness, malleability, ductility, high relative density, and resistance to corrosion seem to make difficult to give up its use. Though Pb widespread use has discontinued in many countries of the world, it is still used in many industries like arm industry, car repair, battery manufacturing and recycling, refining, smelting, etc. [66].

In contrast to organic pollutants the non-biodegradable nature of Pb, as all other chemical elements, is the prime reason for its prolonged persistence in the environment. Due to its non-biodegradable nature and continuous use, Pb concentration accumulates in the environment with increasing hazards [66]. Age-dependent increase of Pb mass fractions in the “normal” prostate tissue indirectly confirm this conclusion. Elevated Pb level is a highly poisonous factor affecting every organ in the body and the prostate gland is not the exclusion.

Thus, according our study for not polluted areas no one influencing factor could explain the variability of published means for prostatic Pb levels from 0.026 mg/kg to 1.60 mg/kg of wet tissue. Moreover, prostate tissue Pb contents showed large variations among individuals (values \pm SD for means in Table 1), 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 Pb 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 1 to 65), and a total of 998 normal controls were investigated from all 26 studies. As such, it is hard to draw definite conclusions about the reference value of the Pb content in “normal” prostate as well as about the clinical value of the Pb levels in “normal” prostates as a biomarker.

Conclusion

The present study is a comprehensive study regarding the determination of Pb content in “normal” human prostates. With this knowledge Pb levels may then be considered as a biomarker for the recognition of prostate disorders. The study has demonstrated that level of Pb in “normal” prostates depends on many factors such as age, dietary Pb intake, and smoking. 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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