



Review Article

Thallium Content of the Normal Human Prostate Gland - A Systematic Review

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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 thallium (Tl) 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 Tl content in the prostatic tissue of healthy subjects. The present study evaluated by systematic analysis the published data for Tl content analyzed in prostatic tissue of "normal" glands. This evaluation reviewed 2087 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 Tl content in prostates of apparently healthy men. The objective analysis was performed on data from the 16 studies, which included 712 subjects. It was found that the range of means of prostatic Tl content reported in the literature for "normal" gland varies widely from 0.00022 mg/kg to 0.1 mg/kg with median of means 0.00027 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: Biomarkers, Human prostate, Normal prostatic tissue, Thallium

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

It was indicated low levels of Tl in human prostatic tissue (0.1 mg/kg of wet tissue) in studies published more than 65 years ago [28]. This finding allowed conclude that the prostate gland accumulates Tl, because the level of metal in prostates was at least three orders of magnitude higher the blood serum reference level (0.00002-0.00034 mg/L) and one order of

magnitude higher the liver reference level (0.01 mg/kg of wet tissue) [29]. Furthermore, experimental data identified that Tl compounds should be considered as genotoxic carcinogens [30]. These findings promoted more detailed studies of the Tl 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 Tl, 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 [31-33]. In this context, until now there are no data on any biological function of Tl in organisms, but a lot of publications testify to adverse health effects in different organs or tissues, including malignancy, of exposure to low doses of this metal and its compounds [30,34-36]. However, it still remains unclear what precise mechanism is responsible for Tl genotoxicity [30].

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

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

Exclusion criteria

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

Data Extraction

A standard extraction of data was applied, and the following available vari-

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

Reference	Method	n	Age range years	Sample preparation	Tl	
					M±SD	Range
Tipton et al. 1954 [28]	AES	1	Adult	D, A	0.1	-
Zakutinsky et al. 1962 [37]	-	-	Adult	-	<0.1	-
Weinig et al. 1967 [38]	MS	1	16	A, AD	0.00024	-
Zaichick et al. 2012 [39]	ICPMS	64	13-60	AD	0.00024±0.00011	0.000034-0.00065
Zaichick et al. 2013 [9]	ICPMS	16	20-30	Intact, AD	0.00051±0.00085	-

ables were extracted from each paper: method of Tl determination, number and ages of healthy persons, sample preparation, mean and median of Tl levels, standard deviations of mean, and range of Tl 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 Tl levels in prostatic tissue. The articles were analyzed and “Median of Means” and “Range of Means” were used to examine heterogeneity of Tl contents. The objective analysis was performed on data from the 16 studies, with 712 subjects.

Results

Information about Tl 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 [26,27,31]. Thus, it dictates a need for reliable values of the Tl 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 2087 publications were primarily obtained, of which 2071 irrelevant papers were excluded. Thus, 16 studies were ultimately selected according to eligibility criteria that investigated Tl levels in tissue of normal prostates (Table 1) and these 16 papers comprised the material on which the review was based [9,13,14,26,28,37-47]. A number of values for Tl 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 [48-54].

Table 1 summarizes general data from the 16 studies. The retrieved studies involved 712 subjects. The ages of subjects were available for 14 studies and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 15 studies. One study determined Tl levels by atomic emission spectrometry (AES), one – by spark mass spectrometry (MS), and thirteen - by inductively coupled plasma mass spectrometry (ICPMS) (Table 1). All methods used were the destructive analytical techniques, because they require sample ashing or acid digestion.

Zaichick et al. 2014 [40]	ICPMS	28	21-40	Intact, AD	0.00024±0.00009	0.000034-0.00041
		27	41-60	Intact, AD	0.00022±0.00010	0.000085-0.00046
		10	61-87	Intact, AD	0.00027±0.00016	0.000051-0.00051
Zaichick et al. 2014 [13]	ICPMS	16	20-30	Intact, AD	0.00023±0.00009	-
Zaichick et al. 2014 [14]	ICPMS	50	0-30	Intact, AD	0.00069±0.0010	-
		29	0-13	Intact, AD	0.00108±0.00133	-
		21	14-30	Intact, AD	0.00027±0.00009	-
Zaichick 2015 [41]	ICPMS	65	21-87	Intact, AD	0.00024±0.00011	-
Zaichick et al. 2016 [42]	ICPMS	28	21-40	Intact, AD	0.00027±0.00014	-
		27	41-60	Intact, AD	0.00029±0.00020	-
		10	61-87	Intact, AD	0.00031±0.00020	-
		37	41-87	Intact, AD	0.00029±0.00019	-
		65	21-87	Intact, AD	0.00029±0.00014	-
Zaichick et al. 2016 [43]	ICPMS	32	44-87	Intact, AD	0.00136±0.00085	-
Zaichick et al. 2016 [44]	ICPMS	37	41-87	Intact, AD	0.00024±0.00010	-
Zaichick et al. 2017 [26]	ICPMS	37	41-87	Intact, AD	0.00024±0.00010	-
Zaichick et al. 2017 [45]	ICPMS	37	41-87	Intact, AD	0,00028±0,00015	0,000062-0,00055
Zaichick 2017 [46]	ICPMS	37	41-87	Intact, AD	0.00023±0.00012	0.000051-0.00051
Zaichick et al. 2019 [47]	ICPMS	37	41-87	Intact, AD	0.00023±0.00012	0.000051-0.00051
Median of means	0.00027					
Range of means ($M_{min} - M_{max}$),	0.00022 - 0.10					
Ratio M_{max}/M_{min}	$(0.10/0.00022) = 455$					
All references	16					

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

AES – atomic emission spectrometry, MS – spark mass spectrometry, ICPMS – inductively coupled plasma mass spectrometry,

D – drying at high temperature, A – ashing, AD – acid digestion.

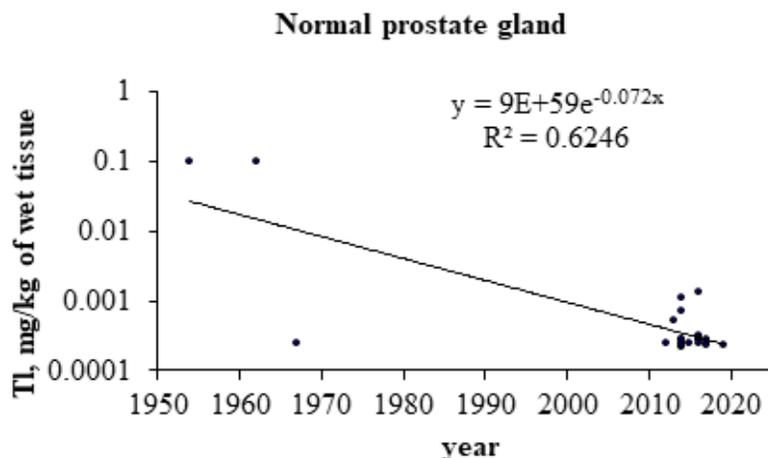


Figure 1: Data on Tl content in normal prostate tissue reported from 1954 to 2020

Discussion

The range of means of Tl mass fractions reported in the literature for “normal” prostatic tissue varies widely from 0.00022 mg/kg to 0.10 mg/kg with median of means 0.00027 mg/kg of wet tissue (Table 1) [28,40]. This variability of reported mean values can be explained a priori by a dependence of Tl content on many factors, including analytical method imperfections, differences in “normal” prostate definitions, possible non-homogeneous distribution of Tl 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 Tl content was measured in pieces of the prostate. Therefore published data allowed us to estimate the effect of only some different factors on Tl content in “normal” prostate tissue.

Analytical Method

The trend line of Tl 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, for example AES, and a lack of quality control of results in old studies published in 50-70s.

In all reported papers destructive analytical methods were used. These methods require 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 [31,55,56]. On the other hand, the Tl 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, but up to now there are no analytical methods which allow to quantify Tl content in “normal” prostate without acid digestion of the samples at a high temperature [57]. It is, therefore, reasonable to conclude that the quality control of results is very important factor for using the Tl 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 Tl content in prostate tissue it was not found a significant changes in Tl content with increasing age [40-42]. These findings allowed us to conclude that the Tl content in “normal” prostates does not depend on age.

Androgen-Independence of Prostatic Tl Levels

There was not found a significant difference between Tl levels in prostates of teenagers before puberty and of post-pubertal teenagers and young adults [9,13,14]. These findings allowed us to conclude that the Tl content in “normal” prostates does not depend on the level of androgens, and vice versa. However, studies on the association between the Tl content in “normal” prostates and the level of androgens in blood were not found.

Tl Intake

The general population can be exposed to low levels of Tl primarily through consumption of food and ingestion of drinking water, and to a lesser degree through inhalation of ambient air [34-36,57]. One may also be exposed to Tl through skin contact with rat poison, semiconductors, fiber optics, and the glass lenses contained Tl or its compounds [57]. Tl exposures were also reported as a result of consumption such drugs as opioids, heroin and cocaine [58]. Another source of exposure to Tl may be smoking [59].

Tl is considered as elements with an extremely high toxic potency for human and animal organisms. The toxicity of this element is higher compared to mercury, cadmium and lead and comparable to that of cyanide [60]. Moreover, Tl is regarded as a latent health hazard with potential risk of toxicity in humans within areas of “natural” contamination by this element [61]. In order to prevent Tl poisoning, its content must not exceed the safe limits for food, drinking water, and air. The safe limits for Tl in a world average daily intake is <0.002 mg/day but in the UK, for example, it was estimated to be approximately 0.005 mg/day [29,61-63]. There is no maximum permissible level (MPL) for Tl in human food, however a value of 0.25±0.5 mg/kg of fresh mass was proposed [64].

Tl contents in dairy products, meat, poultry, eggs, vegetables, fruits and fruit juices, nuts, beverages, and other foods depend on this metal level in soil [34-36,57,64]. There are natural geochemical provinces with anomalous high levels of Tl in soils and areas with mainly anthropogenic sources of Tl contamination, for example, as a result of mining of sulphide liberalization [64]. The MPL for Tl content in agricultural land is 1 mg/kg [65]. Some vegetables such as kale, green cabbage, radish, turnip and watercress can accumulate Tl in concentrations harmful for human health [64-66]. Fish and shellfish is also a known bio-accumulator of Tl [35,67].

Concentration of Tl in waters of different types such as tap water, household wells, groundwater, and surface waters (rivers, lakes, and oceans) variate very widely [68,69]. In US and Europe maximum contaminant level (MCL) in drinking water is 0.002 m/L and there is the goal of lowering the MCL of Tl in drinking water to 0.0005 mg/L [35].

Tl concentration in air can be traced from atmospheric deposition which is varied very widely. For example, in Canadian Arctic the flux of Tl determined in 1998 to 0.00005 mg m⁻²y⁻¹ was two order of magnitude lower than the bulk mass flux in North America 0.005 mg m⁻²y⁻¹ [70].

Tl was historically used in the treatment of malaria, ringworm of the scalp, tuberculosis, typhus, and venereal diseases, including syphilis. Nowadays, the radionuclide ²⁰¹Tl, with a half-life of 73 hours, is used in nuclear medicine for stress tests for risk stratification in patients with coronary artery disease and to differentiate malignant from inflammatory lesions [71].

Historically thallium was leveraged as an insecticide and rodenticide against rats, squirrels, and ants [34,35,64,69]. Many Tl compounds are colorless, odorless and tasteless, and these characteristics, combined with the high toxicity of Tl compounds, have led to their use as poisons [30]. Since its discovery in 1861 it is known that Tl has caused many accidental, occupational and therapeutic poisonings in the entire world.

Tl Content in Body Fluids, Tissues and Organs

Tl rapidly distributes in the various body organs and tissues, generally reaching all cells, because this metal can cross the placental, hematoencephalic, and gonadal barriers [30,35]. It is known that Tl is accumulated primarily in heart, kidneys, large bowel, thyroid, and liver [72]. Tl concentrations in “normal” human urine and blood is very low. Reference

value of Tl concentration in urine for the European unexposed subjects is 0.000006 mg/L [68]. For the general population of the world range of Tl concentration in whole blood was estimated from 0.00015 to 0.00063 mg/L [73,74]. However, in many studies much lower levels of Tl concentration in whole blood of subjects from control groups was found [75,76]. For example, the median concentrations of Tl in whole blood samples of 15-year-old adolescents collected in two cities in Sweden were below the detection limits <0.00006 mg/L [75]. Data on Tl contents in “normal” human organs and tissues are very limited. As usual maximal level of this metal was found in such organs as kidney, brain, and liver. Usual ranges of Tl contents are 0.0005-0.005 mg/kg for kidney, 0.0004-0.002 mg/kg for brain, and 0.0005-0.0015 mg/kg of wet tissue for liver [69,77]. Thus, from these data we can accept 0.00015 mg/L and 0.0005 mg/kg of wet tissue for whole blood and liver, respectively, as the reference values. The median of prostatic Tl content means obtained in the present review (0.00027 mg/kg of wet tissue) almost equals the metal level in liver and approximately two times higher the whole blood level. Thus, we can conclude that the prostate gland is also a target organ for Tl.

All natural chemical elements of the Periodic System, including Tl, present in all subjects of biosphere [31,78,79]. During the long evolutionary period intakes of Tl in organisms were more or less stable and organisms were adapted for such environmental conditions. As was mentioned above, until now there are no data on any biological function of Tl in organisms, but recently inordinately high accumulation of Tl was discovered in two plants *Iberis intermedia* and *Biscutella laevigata* [80]. These plants could contain respectively 0.4% and 1.94% Tl on dry mass basis. Such high accumulation means that these plants not only adopted for Tl level in soil, but they need in this element.

The situation with Tl content in biosphere began to change after the industrial revolution, particularly, over the last 100 years. Nowadays the primary use of Tl is in the sphere of the fiber optic and glass lens industries, the electronics industry for semiconductors, and chemical industries. Common applications of Tl include acousto-optic laser equipment, a catalyst for organic reactions, high-temperature superconductors, specialized temperature-extreme glasses, low-temperature thermometers, infrared light-sensitive photocells, mercury lamps, switches, closures, fuses, radionuclides, detectors of gamma radiation and many other things [63,64]. Thus, inorganic Tl is ubiquitously distributed in environment and food, water, and air everywhere contain this element. In addition to the abundant natural sources of Tl, there are a large number of industrial sources of Tl to the soil (through atmospheric emissions originating from residues from coal, oil, and gas combustion, power plants, cement factories, non-ferrous metal production, brick works, mineral smelters, urban refuse, mine tailings, smelter slag, waste), water (through irrigation and industrial liquid waste, livestock dips, and wastewater sludge application), and air (Tl may be released from residues from coal, oil, and gas combustion, power plants, cement factories, non-ferrous metal production, brick works, mineral smelters, and from combustion of fossil fuels) contamination [63,69,77,81]. In the 2000s the anthropogenic emission of Tl was estimated as 5,000 tons annually [57,69,81,82]. During the 20th century due to the anthropogenic factors Tl content in environment increased in 3 times [83]. From the polluted environment this metal is subsequently introduced into the food chain and for the general population, the food is the main source of exposure to Tl [57,69,81,82].

Tl is an important product in the world industry. The annual world production of Tl has been growing slowly in recent years and reached about 30 tons [57,60,66]. The world's largest producers are Kazakhstan and China. Due to the main applications of Tl in the fibre optics industry and the production of glass lenses, China, Japan and South Korea are the main consumers of this metal. Since the use of Tl is linked to the rapidly developing modern technology, we can assume that over the years, the need of

industry in this metal has increased significantly and would continue to increase in the future.

As mentioned above, an ingestion of Tl low dose by humans can cause a variety of disorders, such as mild gastrointestinal disturbances, polyneuritis, encephalopathy, tachycardia, skin eruptions, stomatitis, atrophic changes of the skin, nail changes, degenerative changes of the heart, liver and kidney, sub-arachnoid hemorrhage, bone marrow depression, alopecia, painful neuropathy, blindness, and others [36,84,85]. Furthermore, as was shown in the experimental studies, Tl compounds are cytotoxic and genotoxic [30,86,87]. Precise molecular mechanisms by which this metal causes healthy cells to transform to malignant states have yet to be fully defined [30].

Thus, according our study for unpolluted areas there are no information could explain the variability of published means for “normal” prostatic Tl levels from 0.00022 mg/kg to 0.10 mg/kg of wet tissue. Moreover, prostate tissue Tl 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 Tl 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 1 to 65), and a total of 712 “normal” prostates were investigated from all 16 studies. As such, it is hard to draw definite conclusions about the reference value of the Tl content in “normal” prostate as well as about the clinical value of the Tl levels in “normal” prostates as a biomarker.

Conclusion

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