LITHIUM LEVEL IN THE PROSTATE OF THE NORMAL HUMAN: A SYSTEMATIC REVIEW

V. Zaichick

Medical Radiological Research Centre, Korolyev St., 4, Obninsk, 249036, Russia

e-mail: vzaichick@gmail.com

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 and TE content ratios in prostate tissue can be used as biomarkers [20–26].

The effects of TEs, including Li (lithium), 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 [27,28].

By now, an exceedingly scant literature exists on quantitative Li 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 Li 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 Li 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 Web of Science, Scopus, PubMed, MEDLINE, ELSEVIER-EMBASE, and Cochrane Library databases, as well as from the personal archive of the author collected between May 1966 to September 2021, using the key words: prostatic trace elements, prostatic Li content, prostatic tissue, and their combinations. For example, the search terms for Li content were: "Li mass fraction", "Li content", "Li level", "prostatic tissue Li" and "Li 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 Li 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 Li levels were measured in samples of prostatic tissue.

Exclusion criteria

Studies were excluded if they were case reports. Studies involving persons from Li contaminated area and subjects that were Li therapeutic or 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 Li determination, number and ages of healthy persons, sample preparation, mean and median of Li levels, standard deviations of mean, and range of Li 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 Li levels in prostatic tissue. The articles were analyzed and “Median of Means” and “Range of Means” were used to examine heterogeneity of Li contents. The objective analysis was performed on data from the 23 studies, with 1190 healthy subjects.

Results

Information about Li 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]. Thus, it dictates a need for reliable values of the Li 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 2312 publications were primarily obtained, of which 2289 irrelevant papers were excluded. Thus, 23 studies were ultimately selected according to eligibility criteria that investigated Li levels in tissue of “normal” prostates (Table 1) and these 23 papers [8, 9, 12, 14, 25, 29–46] comprised the material on which the review was based. A number of values for Li 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% [47–50] and ash – 1% (on a wet mass basis) contents in “normal” prostates of adult men [49,51–53].

Table 1 summarizes general data from the 23 studies. The retrieved studies involved 1190 subjects. The ages of subjects were available for 22 studies and ranged from 0–87 years. Information about the analytical method and sample preparation used was available for 23 studies. All studies determined Li levels by destructive (require acid digestion of tissue samples) analytical methods (Table 1): eight using inductively coupled plasma atomic emission spectrometry (ICP-AES) and nine – inductively coupled plasma mass spectrometry (ICPMS). In five studies a combination of ICP-AES and ICP-MS methods was used and results were summarized.

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

Reference	Method	n	Age, years Range	Li	
				M±SD	Range
Zakutinsky et al. 1962 [29]	–	–	–	0.013	–
Zaichick et al. 2011 [30]	ICP-MS	10	0–10	0.0182±0.0088	0.0053–0.0289
		10	1–20	0.0053±0.0037	0.0026–0.0112
		28	21–40	0.0066±0.0046	0. 0026–0.0165
		27	41–60	0.0070±0.0041	0.0029–0.0170
		8	61–72	0.0075±0.0060	0.0026–0.0172
		83	0–72	0.0088±0.0070	0. 0026–0.0289
Zaichick et al. 2012 [31]	ICP-AES	64	13–60	0.0068±0.0041	0.0026–0.0170
Zaichick et al. 2012 [32[	ICP-MS	64	13–60	0.0068±0.0041	0.0026–0.0170
Zaichick et al. 2013 [8]	ICPAES	16	20–30	0.0068±0.0046	–
Zaichick et al. 2013 [9]	ICPMS	16	20–30	0.0109±0.0083	–
Zaichick et al. 2014b [33]	ICPAES	28	21–40	0.0068±0.0046	0.0026–0.0165
		27	41–60	0.0070±0.0039	0.0029–0.0170
		10	61–87	0.0075±0.0060	0.0026–0.0172
Zaichick et al. 2014 [34]	ICPMS	28	21–40	0.0068±0.0046	0.0026–0.0165
		27	41–60	0.0070±0.0039	0.0029–0.0170
		10	61–87	0.0075±0.0060	0.0026–0.0172
Zaichick et al. 2014 [12]	ICPAES	50	0–30	0.014±0.012	–
		29	0–13	0.020±0.014	–
		21	14–30	0.0088±0.0056	–
Zaichick et al. 2014 [35]	ICPMS	50	0–30	0.014±0.012	–
		29	0–13	0.020±0.014	–
		21	14–30	0.0084±0.0058	–
Zaichick et al. 2014 [14]	2 Methods	16	20–30	0.0068±0.0046	–
Zaichick 2015 [36]	2 Methods	65	21–87	0.0070±0.0044	–
Zaichick et al. 2016 [37]	ICPAES	28	21–40	0.0080±0.0079	–
		27	41–60	0.0086±0.0062	–
		10	61–87	0.0087±0.0076	–
Zaichick et al. 2016 [38]	ICPMS	28	21–40	0.0080±0.0079	–
		27	41–60	0.0086±0.0062	–
		10	61–87	0.0087±0.0076	–
Zaichick et al. 2016 [39]	ICPAES	37	41–87	0.0071±0.0044	0.0026–0.0172
Zaichick et al. 2016 [40]	ICPAES	32	44–87	0.0073±0.0046	0.0026–0.0172
Zaichick et al. 2016 [41]	ICPAES	37	41–87	0.0071±0.0044	0.0026–0.0172
Zaichick et al. 2016 [42]	ICPMS	32	44–87	0.0072±0.0055	–
Zaichick et al. 2016 [43]	ICPMS	37	41–87	0.0071±0.0056	–
Zaichick et al. 2017 [25]	ICPMS	37	41–87	0.0071±0.0056	–
Zaichick et al. 2017 [44]	2 Methods	37	41–87	0.0082±0.0049	0.00284–0.0190
Zaichick 2017 [45]	2 Methods	37	41–87	0.0071±0.0045	0.0026–0.0172
Zaichick et al. 2019 [46]	2 Methods	37	41–87	0.0071±0.0045	0.0026–0.0172
Median of means				0.0074	
Range of means (M_{min} - M_{max}),				0.0068–0.0200	
Ratio M_{max}/M_{min}				(0.0200/0.0068)=2.94	
All references				23	

Discussion

The range of means of Li mass fractions reported in the literature for “normal” prostatic tissue varies from 0.0068 mg/kg [33] to 0.020 mg/kg [35] with median of means 0.0074 mg/kg of wet tissue (Table 1). The maximal value of mean Li mass fraction reported [35] was 2.94 times higher the minimal published Li mass fraction (Table 1).

This variability of reported mean values can be explained by a dependence of Li content on many factors, including analytical method imperfections, differences in “normal” prostate definitions, possible non-homogeneous distribution of Li levels throughout the prostate gland volume, diet, smoking, alcohol intake and others. Not all these factors were strictly controlled in the cited studies.

In our opinion, the leading cause of inter-observer Li content variability was the need for sample destruction. In 22 of 23 reported papers such destructive analytical methods as ICP-AES 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 [24,54,55]. On the other hand, the Li 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 Li 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 Li content in prostatic tissue as biomarkers.

All natural chemical elements of the Periodic System, including Li, present in all subjects of biosphere [27,56,57]. During the long evolutional period intakes of Li 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. The situation began to change after the industrial revolution, particularly, over the last 100 years. The primary use of Li is in industry and medicine. Thus, inorganic Li is ubiquitously distributed in environment and food, water, and air everywhere contain this element. In addition to the abundant natural sources of Li, there are a large number of industrial and pharmaceutical sources of Li to the soil, water, and air (through atmospheric industrial emissions) contamination. From the polluted environment Li is subsequently introduced into the food chain and food is the major source of human exposure to Li.

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 10 to 65), and 22 of 23 studies were done one team. As such, it is hard to draw definite conclusions about the reference value of the Li content in “normal” prostate as well as about the clinical value of the Li levels in “normal” prostates as a biomarker.

References

1. Nickel J.C. (2011) Prostatitis. Can. Urol. Assoc. J. **5**:306–315.
2. Lim K.B. (2017) Epidemiology of clinical benign prostatic hyperplasia. Asian J. Urol. **4**:148–151.
3. Rawla P. (2019) Epidemiology of prostate cancer. World J. Oncol. **10**(2):63–89.

4. Avisyn A.P., Dunchik V.N., Zhavoronkov A.A., Zaichick V.E., Sviridova T.V. (1981) Histological structure of the prostate and content of zinc in it during various age period. Archiv Anatomy, Gistology, and Ebriology (Leningrad) **81**(11):76–83.
5. Zaichick V. (2004) INAA and EDXRF applications in the age dynamics assessment of Zn content and distribution in the normal human prostate. J. Radioanal Nucl. Chem. **262**:229–234.
6. Zaichick V., Zaichick S. (2013) The effect of age on Br, Ca, Cl, K, Mg, Mn, and Na mass fraction in pediatric and young adult prostate glands investigated by neutron activation analysis. Appl. Radiat. Isot. **82**:145–151.
7. Zaichick V., Zaichick S. (2013) INAA application in the assessment of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn mass fraction in pediatric and young adult prostate glands. J. Radioanal Nucl. Chem. **298**:1559–1566.
8. Zaichick V., Zaichick S. (2013) NAA-SLR and ICP-AES application in the assessment of mass fraction of 19 chemical elements in pediatric and young adult prostate glands. Biol. Trace Elem. Res. **156**:357–366.
9. Zaichick V., Zaichick S. (2013) Use of neutron activation analysis and inductively coupled plasma mass spectrometry for the determination of trace elements in pediatric and young adult prostate. Am. J. Analyt. Chem. **4**:696–706.
10. Zaichick V., Zaichick S. (2014) Relations of bromine, iron, rubidium, strontium, and zinc content to morphometric parameters in pediatric and nonhyperplastic young adult prostate glands. Biol. Trace Elem. Res. **157**:195–204.
11. Zaichick V., Zaichick S.(2014) Relations of the neutron activation analysis data to morphometric parameters in pediatric and nonhyperplastic young adult prostate glands. Advances in Biomedical Science and Engineering **1**:26–42.
12. Zaichick V., Zaichick S. (2014) Relations of the Al, B, Ba, Br, Ca, Cl, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr, and Zn mass fractions to morphometric parameters in pediatric and nonhyperplastic young adult prostate glands. BioMetals **27**:333–348.
13. Zaichick V., Zaichick S. (2014) The distribution of 54 trace elements including zinc in pediatric and nonhyperplastic young adult prostate gland tissues. Journal of Clinical and Laboratory Investigation Updates **2**(1):1–15.
14. Zaichick V., Zaichick S. (2014) Androgen-dependent chemical elements of prostate gland. Androl. Gynecol.: Curr. Res. 2:2.
15. Zaichick V., Zaichick S. (2015) Differences and relationships between morphometric parameters and zinc content in nonhyperplastic and hyperplastic prostate glands. Br. J. Med. & Med. Res. **8**:692–706.
16. Schwartz M.K. (1975) Role of trace elements in cancer. Cancer Res. **35**:3481–3487.
17. Zaichick V., Zaichick S. (1999) Role of zinc in prostate cancerogenesis. In: Mengen und Spurenelemente. 19. Arbeitstagung. Friedrich-Schiller-Universitat, Jena, pp 104–115.
18. Zaichick V., Zaichick S. Wynchank S. (2016) Intracellular zinc excess as one of the main factors in the etiology of prostate cancer. J. Anal. Oncol. **5**:124–131.
19. Zaichick V., Zaichick S., Rossmann M. (2016) Intracellular calcium excess as one of the main factors in the etiology of prostate cancer. AIMS Mol. Sci. **3**:635–647.
20. Dunchik V., Zherbin E., Zaichick V., Leonov A., Sviridova T. (1980) Method for differential diagnostics of prostate malignant and benign tumours. Russian patent (Author's Certificate No 764660, priority of invention 27.10.1977). Discoveries, Inventions, Commercial Models, Trade Marks 35:13.
21. Zaichick V., Sviridova T., Zaichick S. (1997) Zinc in the human prostate gland: normal, hyperplastic and cancerous. Int. Urol. Nephrol. **29**:565–574.
22. Zaichick V., Sviridova T., Zaichick S. (1997) Zinc in human prostate gland: normal, hyperplastic and cancerous. J. Radioanal. Nucl. Chem. **217**:157–161.

23. Zaichick S., Zaichick V. (2012) Trace elements of normal, benign hypertrophic and cancerous tissues of the human prostate gland investigated by neutron activation analysis. J. Appl. Radiat. Isot. **70**:81–87.
24. Zaichick V., Zaichick S. (2016) Ratios of selected chemical element contents in prostatic tissue as markers of malignancy. Hematol. Med. Oncol. **1**(2):1–8.
25. Zaichick V., Zaichick S. (2017) Trace element levels in prostate gland as carcinoma's markers. J. Cancer Ther. **8**:131–145.
26. Zaichick V., Zaichick S. (2017) Ratios of Zn/trace element contents in prostate gland as carcinoma's markers. Cancer Rep. Rev. **1**(1):1–7.
27. Zaichick V. (2006) Medical elementology as a new scientific discipline. J. Radioanal. Nucl. Chem. **269**:303–309.
28. Enderle J., Klink U., di Giuseppe R., Koch M., Seidel U., Weber K., Birringer M., Ratjen I., Rimbach G., Lieb W. (2020) Plasma lithium levels in a general population: a cross-sectional analysis of metabolic and dietary correlates. Nutrients **12**(8):2489.
29. Zakutinsky D.I., Parfyenov Yu.D., Selivanova L.N. (1962) Data book on the radioactive isotopes toxicology. State Publishing House of Medical Literature, Moscow.
30. Zaichick S., Zaichick V., Karandashev V., Nosenko C., Ermidou-Pollet S., Pollet S. (2011) The effect of age on the lithium content in prostate of healthy men. In: Interaction of Neutrons with Nuclei. Joint Institute for Nuclear Research, Dubna, Moscow Region, Russia, pp. 337–341.
31. Zaichick V., Nosenko S., Moskvina I. (2012) The effect of age on 12 chemical element contents in intact prostate of adult men investigated by inductively coupled plasma atomic emission spectrometry. Biol. Trace Elem. Res. **147**:49–58.
32. Zaichick S., Zaichick V., Nosenko S., Moskvina I. (2012) Mass fractions of 52 trace elements and zinc trace element content ratios in intact human prostates investigated by inductively coupled plasma mass spectrometry. Biol. Trace Elem. Res. **149**:171–183.
33. Zaichick V., Zaichick S. (2014) Determination of trace elements in adults and geriatric prostate combining neutron activation with inductively coupled plasma atomic emission spectrometry. Open Journal of Biochemistry **1**(2):16–33.
34. Zaichick V., Zaichick S. (2014) Use of INAA and ICP-MS for the assessment of trace element mass fractions in adult and geriatric prostate. J. Radioanal. Nucl. Chem .**301**(2):383–397.
35. Zaichick V., Zaichick S. (2014) The distribution of 54 trace elements including zinc in pediatric and nonhyperplastic young adult prostate gland tissues. Journal of Clinical and Laboratory Investigation Updates **2**(1):1–15.
36. Zaichick V. (2015) The variation with age of 67 macro- and microelement contents in nonhyperplastic prostate glands of adult and elderly males Investigated by nuclear analytical and related methods. Biol. Trace Elem. Res. **168**:44–60.
37. Zaichick V., Zaichick S. (2016) Age-related changes in concentration and histological distribution of 18 chemical elements in nonhyperplastic prostate of adults. World Journal of Pharmaceutical and Medical Research **2**(4):5–18.
38. Zaichick V., Zaichick S.(2016) Age-related changes in concentration and histological distribution of 54 trace elements in nonhyperplastic prostate of adults. Int. Arch. Urol. Complic. **2**(2):019.
39. Zaichick V., Zaichick S. (2016) The comparison between the contents and interrelationships of 17 chemical elements in normal and cancerous prostate gland. JPS Open Access 1(1):1–10.
40. Zaichick V., Zaichick S. (2016) Prostatic tissue level of some major and trace elements in patients with BPH. J.J. Nephro. Urol. **3**(1):1–10.
41. Zaichick V., Zaichick S. (2016) Distinguishing malignant from benign prostate using content of 17 chemical elements in prostatic tissue. Integr. Cancer Sci. Therap. **3**(5):579–587.
42. Zaichick S., Zaichick V. (2016) Prostatic tissue levels of 43 trace elements in patients with BPH. British Journal of Medicine & Medical Research **15**(2):1–12.
43. Zaichick V., Zaichick S. (2016) Prostatic tissue levels of 43 trace elements in patients with prostate adenocarcinoma. Cancer and Clinical Oncology **5**(1):79–94.

44. Zaichick V., Zaichick S. (2017) Chemical element contents in normal and benign hyperplastic prostate. Ann. Men Health Wellness **1**(2):1006.
45. Zaichick V. (2017) Differences between 66 Chemical Element Contents in Normal and Cancerous Prostate. Journal of Analytical Oncology **6**:37–56.
46. Zaichick V., Zaichick S. (2019) Comparison of 66 chemical element contents in normal and benign hyperplastic prostate. Asian Journal of Urology **6**:275–289.
47. Isaacs J.T. (1983) Prostatic structure and function in relation to the etiology of prostatic cancer. The Prostate **4**(4):351–366.
48. Leissner K.M., Fielkegard B., Tisell L.E. (1980) Concentration and content of zinc in human prostate. Invest. Urol. **18**:32–35.
49. Woodard H.Q., White D.R. (1986) The composition of body tissues. Br.J. Radiol. **59**:1209–1218.
50. Arnold W.N., Thrasher J.B. (2003) Selenium concentration in the prostate. Biol. Trace Elem. Res. **91**(3):277–280.
51. Tipton I.H., Cook M.J. (1963) Trace elements in human tissue. Part II. Adult subjects from the United States. Health Phys. **9**:103–145.
52. Schroeder H.A., Nason A.P., Tipton I.H., Balassa J.J. (1967) Essential trace metals in man: Zinc. Relation to environmental cadmium. J. Chron. Dis. **20**:179–210.
53. Saltzman B.E., Gross S.B., Yeager D.W., Meiners B.G., Gartside P.S. (1990) Total body burdens and tissue concentrations of lead, cadmium, copper, zinc, and ash in 55 human cadavers. Environ. Res. **52**:126–145.
54. Zaichick V. (1997) Sampling, sample storage and preparation of biomaterials for INAA in clinical medicine, occupational and environmental health. In: Harmonization of Health-Related Environmental Measurements Using Nuclear and Isotopic Techniques. IAEA, Vienna, pp 123–133.
55. Zaichick V. (2004) Losses of chemical elements in biological samples under the dry ashing process. Trace Elements in Medicine (Moscow) **5**(3):17–22.
56. Vernadsky V.I .(1978) Living Matter, Nauka, Moscow.
57. Zaichick V., Ermidou-Pollet S., Pollet S. (2007) Medical elementology: a new scientific discipline. Trace Elements and Electrolytes **24**(2):69–74.