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Comparison between Bromine, Calcium, Chlorine, Iodine, Potassium, Magnesium, Manganese, and Sodium Contents in Normal Thyroid and Riedel's Struma

Vladimir Zaichick

Radionuclide Diagnostics Department, Medical Radiological Research Centre, Russia

ABSTRACT

Role of chemical elements (ChE) in etiology and pathogenesis of Riedel's disease (RD) is unclear. The aim of this exploratory study was to assess whether there were significant changes in thyroid tissue levels of eight ChE (Br, Ca Cl, I, K, Mg, Mn, and Na) are present in the fibrotic transformed thyroid. Eight ChE of thyroid tissue were determined in 6 patients with RD. The control group included thyroid tissue samples from 105 healthy individuals. Measurements were conducted using non-destructive instrumental neutron activation analysis with high-resolution spectrometry of short-lived radionuclides. Reduced mean values of Ca and I content in 6.3 and 6.7 times, respectively, while elevated level of Br in 5.1 times were found in thyroid with RD in comparison with normal level. Because considerable changes in some ChE contents in tissue of thyroid with RD were found, it is reasonable to assume that the levels of these ChE in affected thyroid tissue can be used as RD markers. However, this topic needs additional studies.

***Corresponding author**

Prof. Dr. Vladimir Zaichick, PhD, DSc, CChem, FRSC, Korolyev St. 4, MRRC, Obninsk 249036, Kaluga region, Russia, Tel: +7(48439) 60289; E-mail: vzaichick@gmail.com

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Introduction

Riedel's struma, also called Riedel's disease and Riedel's thyroiditis. is a peculiarly hard, infiltrative lesion (nodule) of the thyroid gland [1]. Riedel's disease (RD) is a rare form of chronic thyroiditis of unknown etiology associated with global or partial fibrosis of the thyroid gland, destruction of the thyroid follicle architecture, obliterative phlebitis, and a mixed infiltrate of lymphocytes, eosinophils, and plasma cells [1,2]. Clinical differentiation between RD, Hashimoto's disease, and other thyroid benign and malignant nodules is often difficult [2,3]. We hypothesized that disbalance of trace elements (TE) contents in thyroid tissue may play a significant role in etiology and pathogenesis of RD. Furthermore, specific levels of TE contents in fibrotic transformed thyroid tissue may be used as RD biomarkers.

For over the 20th century, there was the governing opinion that all thyroid nodules (TN), including RD, are the straightforward sequel of iodine (I) deficiency. Though, it was found that TN is a frequent disease even in those countries and regions where the inhabitants are never exposed to I shortage [4]. Moreover, it was shown that iodine excess has severe effects on human health and is associated with the development of thyroidal disfunctions and autoimmunity, nodular and diffuse goiter, benign and malignant tumors of gland [5-8]. It was also demonstrated that besides the iodine deficiency and excess many other dietary, environmental, and occupational factors are associated with the TN incidence [9-11]. Among them, a disruption of evolutionary stable input of many chemical elements (ChE) in the human body after the industrial revolution plays a significant role in the etiology of thyroidal disorders [12].

In addition to I, many other ChE is involved in essential physiological functions. Crucial or toxic (goitrogenic, mutagenic, carcinogenic) properties of ChE depend on tissue-specific need or tolerance, respectively. Deficiency, overload, or an imbalance of the ChE may result in cellular dysfunction, degeneration, death, benign or malignant transformation [13-15].

In our earlier studies, the complex of in vivo and in vitro nuclear analytical and related methods was developed and used for the investigation of iodine and other ChE contents in the normal and pathological thyroid [16-22]. Iodine level in the normal thyroid was scrutinized in relation to age, gender, and some non-thyroidal diseases [23,24]. Hereafter, variations of ChE content with age in the thyroid of males and females were studied, and age- and gender-dependence of some ChE was perceived [25-41]. In addition, a significant difference between some ChE contents in normal and cancerous thyroid was demonstrated [42-47].

So far, the etiology and pathogenesis of RD has to be considered as multifactorial. The present study was performed to clarify the role of some ChE in the RD etiology. Having this in mind, we focused on assessing the bromine (Br), calcium (Ca), chlorine (Cl), I, potassium (K), magnesium (Mg), manganese (Mn), and sodium (Na) contents in normal thyroid (NT) and in thyroid gland with

RD using non-destructive instrumental neutron activation analysis with high-resolution spectrometry of short-lived radionuclides (INAA-SLR). A further objective was to compare the levels of these ChE in the NT and RD groups of samples.

Material and Methods

All patients with RD (n=6, 5 females and 1 male, mean age M±SD was 39±9 years, range 34-50) were hospitalized in the Head and Neck Department of the Medical Radiological Research Centre (MRRC), Obninsk. Thick-needle puncture biopsy of suspicious lesion of the gland was performed for every persons, to allow morphological examination of affected thyroid tissue and to determine their TE contents. For all patients the diagnosis has been confirmed by clinical and morphological results obtained during studies of biopsy and resected materials. Histological conclusion for all thyroidal lesions was the RD.

Normal thyroids for the control group samples were drawn out at necropsy from 105 deceased (mean age 44±21 years, range 2-87), who had died suddenly. The majority of deaths were owing to trauma. A histological examination in the control group was used to control the age norm conformity, also to confirm the absence of micro-nodules and latent cancer.

All studies were approved by the Ethical Committees of the MRRC, All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or with comparable ethical standards.

All tissue samples were divided into two parts using a titanium scalpel [48]. One was used for morphological study, while the other was for ChE analysis. After the samples intended for ChE analysis were weighed, they were freeze-dried and homogenized [49]. The pounded samples weighing about 10 mg (for biopsy) and 100 mg (for resected materials) were used for ChE measurement by INAA-SLR.

Details of sample preparation, activation by neutrons of nuclear reactor, gamma-spectrometry, calibration with biological synthetic standards, and quality insurance using certified reference material (CRM) of International Atomic Energy Agency (IAEA) CRM IAEA H-4 (animal muscle) were presented in our earlier publications concerning the INAA-SLR of ChE contents in human thyroid [18,27,28,50].

A dedicated computer program for INAA-SLR mode optimization was used [51]. All the thyroid samples were prepared in duplicate, and mean values of ChE contents were used in the final calculation. Using Microsoft Office Excel, a summary of the statistics, including arithmetic mean, standard deviation, standard error of the mean, minimum and maximum values, median, percentiles with 0.025 and 0.975 levels was calculated for ChE contents in NT and RD groups of tissue samples. The difference in the results between two groups (NT and RD) was evaluated by the parametric Student's t-test and non-parametric Wilcoxon-Mann-Whitney U-test.

Results

Table 1 presents certain statistical parameters of the Br, Ca Cl, I, K, Mg, Mn, and Na mass fraction in normal thyroid and Riedel's struma. Comparison of values obtained for Br, Ca, Cl, I, K, Mg, Mn, and Na contents in the NT samples with median of means reported by other researches [52-64] depicts in Table 2. A number of values for ChE mass fractions in literature were not expressed on a dry mass basis. However, we calculated these values using published data for water (75%) [65] and ash (4.16% on dry mass basis) [66] contents in thyroid of adults. The ratios of means and the distinction between mean values of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions in normal thyroid and Riedel's struma are presented in Table 3.

Table 1: Some statistical parameters of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in normal thyroid and Riedel's struma

Tissue	Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Normal thyroid n=105	Br	16.3	11.6	1.3	1.90	66.9	13.6	2.57	51.0
	Ca	1692	1022	109	414	6230	1451	460	3805
	Cl	3400	1452	174	1030	6000	3470	1244	5869
	I	1841	1027	107	114	5061	1695	230	4232
	K	6071	2773	306	1740	14300	5477	2541	13285
	Mg	285	139	16.5	66.0	930	271	81.6	541
	Mn	1.35	0.58	0.07	0.510	4.18	1.32	0.537	2.23
	Na	6702	1764	178	3050	13453	6690	3855	10709
Riedel's struma n=6	Br	88.5	39.0	19.5	38.0	123	96.5	41.0	122
	Ca	279	238	168	111	447	279	119	439
	Cl	6252	3722	2149	3499	10487	4769	3563	10201
	I	276	283	115	85	824	164	85.6	762
	K	12667	7652	4418	6612	21264	10111	6787	20706
	Mg	497	241	139	306	768	418	312	751
	Mn	2.05	1.30	0.75	0.57	3.92	2.57	0.67	3.00
	Na	6332	3642	2103	3732	10494	4769	3784	10208

M – arithmetic mean, SD – standard deviation, SEM – standard error of mean, Min – minimum value, Max – maximum value, P 0.025 – percentile with 0.025 level, P 0.975 – percentile with 0.975 level.

Table 2: Median, minimum and maximum value of means Br, Ca, Cl, I, K, Mg, Mn, and Na contents in normal and goitrous thyroid according to data from the literature in comparison with our results (mg/kg, dry mass basis)

Tissue	Element	Published data [Reference]			This work
		Median of means (n)*	Minimum of means M or M±SD, (n)**	Maximum of means M or M±SD, (n)**	M±SD
Normal	Br	18.1 (11)	5.12 (44) [52]	284±44 (14) [53]	16.3±11.6
	Ca	1600 (17)	840±240 (10) [54]	3800±320 (29) [54]	1692±1022
	Cl	6800 (5)	804±80 (4) [55]	8000 (-) [56]	3400±1452
	I	1888 (95)	159±8 (23) [57]	5772±2708 (50) [58]	1841±1027
	K	4400 (16)	46.4±4.8 (4) [55]	6090 (17) [59]	6071±2773
	Mg	390 (16)	3.5 (-) [60]	1520 (20) [61]	285±139
	Mn	1.62 (40)	0.076 (83) [62]	69.2±7.2 (4) [55]	1.35±0.58
	Na	8000 (9)	438 (-) [63]	10000±5000 (11) [64]	6702±1764

M –arithmetic mean, SD – standard deviation, (n)* – number of all references, (n)** – number of samples.

Table 3: Differences between mean values (M±SEM) of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in normal thyroid and Riedel's struma

Element	Thyroid tissue				Ratio
	Normal thyroid n=105	Riedel's struma n=6	Student's t-test *p*<	U-test *p*	Riedel's struma to Normal thyroid
Br	16.3±1.3	88.5±19.5	**0.0338**	**≤0.01**	5.43
Ca	1692±109	279±168	**0.0187**	**≤0.01**	0.16
Cl	3400±174	6252±2149	0.316	>0.05	1.84
I	1841±107	276±115	**0.00000001**	**≤0.01**	0.15
K	6071±306	12667±4418	0.274	>0.05	2.09
Mg	285±17	497±139	0.265	≤0.05	1.74
Mn	1.35±0.07	2.05±0.75	0.451	>0.05	1.52
Na	6702±1785	6332±2103	0.877	>0.05	0.94

M – arithmetic mean, SEM – standard error of mean, Significant values are in **bold**.

Discussion

Previously found good agreement of the Br, Ca, Cl, I, K, Mg, Mn, and Na contents analyzed by INAA-SLR with the certified data of CRM IAEA H-4 [18,27,28,50] indicates an acceptable accuracy of the results obtained in the study of ChE of the thyroid samples presented in Tables 1-3. The mean values and all selected statistical parameters were calculated for all eight ChE (Br, Ca, Cl, I, K, Mg, Mn, and Na) mass fractions in NT and RD group of samples (Table 1). In a general sense values obtained for Br, Ca, Cl, I, K, Mg, Mn, and Na contents in the NT samples (Table 2) agree well with median of mean values reported by other researches [52-64]. Data cited in Table 2 for NT also includes samples obtained from patients who died from different non-endocrine diseases. In our previous study it was shown that some non-endocrine diseases can effect on TE contents in thyroid [24]. Moreover, in many studies the "normal" thyroid means a visually non-affected tissue adjacent to benign or malignant thyroidal nodules. However, there are no data on a comparison between the ChE contents in such kind of samples and those in thyroid of healthy persons, which permits to confirm their identity.

The data on ChE levels in RD tissue were not found in the literature.

The range of means of Br, Ca, Cl, I, K, Mg, Mn, and Na level reported in the literature for NT tissue vary widely (Table 2). This can be explained by a dependence of ChE content on many factors, including "normality" of thyroid samples (see above), the region of the thyroid, from which the sample was taken, age, gender, ethnicity, mass of the gland, and its functional activity. Not all these factors were strictly controlled in cited studies. However, in our opinion, the main reason for the inter-observer discrepancy can be attributed to the accuracy of the analytical techniques, sample preparation methods, and the inability to take standardized samples from affected tissues. It was insufficient quality control of results in these studies. In many scientific reports, tissue samples were ashed or dried at high temperature for many hours. In other cases, thyroid samples were treated with solvents (distilled water, ethanol, formalin etc). There is evidence that during ashing, drying and digestion at high temperature some quantities of certain ChE are lost as a result of this treatment. That concerns not only such volatile halogen as Br, but also other ChE investigated in the study [67,68].

From Table 3, it is observed that in RD samples the mass fraction of Ca and I are approximately 6.3 and 6.7 times, respectively, lower, while Br content 5.4 times higher than in NT. Thus, if we accept the ChE contents in the NT group as a norm, we have to conclude that with a fibrotic transformation the Br, Ca, and I level in thyroid tissue notably changed.

Characteristically, elevated or reduced levels of ChE observed in affected tissues are discussed in terms of their potential role in the initiation and promotion of TN. In other words, using the low

or high levels of the ChE in TN researchers try to determine the role of the deficiency or excess of each ChE in the TN etiology. In our opinion, abnormal levels of many ChE in TN, including RD, could be and cause, and also effect of thyroid tissue transformation. From the results of such kind studies, it is not always possible to decide whether the measured decrease or increase in ChE level in pathologically altered tissue is the reason for alterations or vice versa. Nevertheless the differences between ChE levels in normal and affected thyroid tissue could be used as RD markers.

This study has some limitations. Firstly, analytical techniques used in this study measure merely eight ChE (Br, Ca, Cl, I, K, Mg, Mn, and Na) mass fractions. Future studies should be aimed toward using other analytical methods which will elongate the list of ChE investigated in NT and RD. Secondly, the sample size of RD group was relatively small and prevented investigations of ChE contents in RD group using differentials like gender, thyroid functional activity, stage of disease, dietary habits of healthy persons and patients with RD. Lastly, the generalization of our outcomes may be bounded to the Russian population. Despite these limitations, this study provides evidence on fibrotic-specific tissue Br, Ca, and I level alteration and shows the necessity to continue ChE research of RD.

Conclusion

In this work, ChE analysis was carried out in the tissue samples of NT and RD using INAA-SLR. It was shown that INAA-SLR is an adequate analytical tool for the non-destructive determination of Br, Ca, Cl, I, K, Mg, Mn, and Na content in the tissue samples of human thyroid in norm and pathology, including needle-biopsy samples. It was perceived the considerable changes in ChE contents in the fibrotic transformed tissue of thyroid. In our opinion, the presented study data strongly suggest that ChE play an important role in thyroid health, as well as in the etiology and pathogenesis of RD. It was assumed that the differences in Br, Ca, and I levels in affected thyroid tissue could be used as RD markers.

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Disclosure

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