RESEARCH ARTICLE

Comparison Between Bromine, Calcium, Chlorine, Iodine, Potassium, Magnesium, Manganese, and Sodium Contents in Normal Thyroid and Thyroid with Hashimoto's Thyroiditis

Vladimir Zaichick

Radionuclide Diagnostics Department, Medical Radiological Research Centre, Russia

ABSTRACT

Purpose: Role of chemical elements (ChE) in etiology and pathogenesis of Hashimoto's thyroiditis (HT) 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 autoimmune transformed thyroid. **Methods:** Eight ChE of thyroid tissue were determined in 8 patients with HT and 105 healthy populations. The measurements were performed using non-destructive instrumental neutron activation analysis with high-resolution spectrometry of short-lived radionuclides. **Results:** It was found that in thyroid with HT the mean contents of Ca and I are 43% and 48%, respectively, lower, while the mass fraction of Br is almost 5 times higher than in NT. **Conclusion:** There are considerable changes in some ChE contents in tissue of thyroid with HT. Thus, it is reasonable to assume that the levels of these ChE in thyroid tissue can be used as HT markers. However, this topic needs additional studies.

Key words: Hashimoto's thyroiditis, Intact thyroid, Trace elements, Energy-dispersive X-ray fluorescent analysis.

INTRODUCTION

Hashimoto's thyroiditis (HT), also called chronic lymphocytic or autoimmune thyroiditis, is part of the spectrum of chronic autoimmune thyroid diseases [1]. Hashimoto's disease is associated with thyroid autoantibodies production like the most common, thyroid peroxidase and thyroglobulin antibodies, and with lymphocytic inltration [1]. Although the HT was described over 100 years ago the exact mechanism of progressive thyroid tissue destruction as a result of HT is still not sufficiently elucidated. Clinical differentiation between HT, Riedel's struma and other thyroid benign and malignant nodulesis often difficult [2,3]. We hypothesized that disbalance of chemical elements (ChE) contents in thyroid tissue may play a significant role in etiology and pathogenesis of HT. Furthermore, specific levels of ChE contents in autoimmune transformed thyroid tissue may be used as HT biomarkers.

For over 20th century, there was the dominant opinion that all thyroid nodules (TN), including HT, are the elementary consequence of iodine (I) deficiency. However, TN have been found to be a frequent disease even in those countries and regions where the population is never exposed to I deficiency [4]. Moreover, it was shown that iodine excess has severe effects on human health and associated with the development

Address for correspondence:
Dr. V. Zaichick, Medical Radiological Research Centre Korolyev St.4, Obninsk 249036, KalugaRegion, Russia.
Tel: +7 (48439) 60289

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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 HT incidence [9-11]. Among them a disturbance of evolutionary stable input of many ChE in human body after industrial revolution plays a significant role in etiology of thyroidal disorders [12].

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

In our previous studies the complex of in vivo and in vitro nuclear analytical and related methods was developed and employed for the investigation of I and other ChE levels in the normal and pathological thyroid gland [16-22]. Level of I in the normal gland was studied in relation to age, gender and some non-thyroidal diseases [23,24]. After that, variations of many other ChE content with age in the thyroid of males and females were investigated and age- and gender-dependence of some ChE was observed [25-41]. Furthermore, a significant difference between some ChE mass fractions in normal and malignant thyroid was demonstrated [42-47].

So far, the etiology and pathogenesis of HT has to be considered as multifactorial. The present study was performed to clarify the role of some ChE in the HT etiology. Having this in mind, we focusedon assessing the bromine (Br), calcium (Ca), chlorine (Cl), I, potassium (K), magnesium (Mg), manganese (Mn), and sodium (Na) contents normal thyroid tissue (NT) and HT affected gland using non-destructive instrumental neutron activation analysis with high-resolution spectrometry of short-lived radionuclides (INAA-SLR). A further aim was to compare the levels of these ChE in the NT and HT groups of samples.

MATERIAL AND METHODS

All patients with HT(n=8, 7 females and 1 male, mean age M±SD was 40±10 years, range 34-55) 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 HT.

Normal thyroid samples were removed at necropsy from 105 deceased (mean age 44±21 years, range 2-87), who had died suddenly. The majority of deaths were due to trauma. Histological examination was used in the NT group to match the age criteria, as well as to confirm the absence of micro-nodules and underlying cancer.

All thyroid samples were divided into two parts using a titanium scalpel [48]. One was used for morphological study while the other was for ChE evaluation. All samples for ChE analysis were weighed, 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 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 HT groups of tissue samples. The difference in the results between two groups (NT and HT) was evaluated by the parametric Student's *t*-test and non-parametricWilcoxon-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 thyroid with Hashimoto's thyroiditis.

Comparison of values obtained for Br, Ca, Cl, I, K, Mg, Mn, and Na contents in the NT and HT samples with median of means reported by other researches [9,52-67] depicts in Table 2.

The ratios of means and the difference between mean values of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions in normal thyroid and thyroid with Hashimoto's thyroiditis are presented in Table 3.

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 eight ChE (Br, Ca, Cl, I, K, Mg, Mn, and Na) mass fractions (Table 1).

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 thyroid with Hashimoto's thyroiditis.

Tissue	Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Normal	Br	16.3	11.6	1.3	1.90	66.9	13.6	2.57	51.0
n=105	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
Hashimoto's	Br	81.3	38.1	22.0	55.0	125	64.0	55.5	122
thyroiditis	Ca	971	197	114	775	1169	968	785	1159
n=8	Cl	8068	2571	1818	6250	9886	8068	6341	9795
	I	951	630	222	83.0	1787	1136	120	1759
	K	11785	9731	5618	5690	23007	6657	5738	22190
	Mg	530	276	159	326	844	419	331	823
	Mn	2.60	2.33	1.35	0.930	5.26	1.60	0.964	5.08
	Na	10211	1432	827	9286	11861	9486	9296	11742

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.

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]. A number of values for TE mass fractions in literature were not expressed on a dry mass basis. However, we calculated these values using published data for water (75%) [68] and ash (4.16% on dry mass basis) [69] contents in thyroid of adults.

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

Tissue	El	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
thyroid	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
Hashimoto's	Br	-	-	-	81.3±38.1
thyroiditis	Ca	-	-	-	971±197
	Cl	-	-	-	8068±2571
	I	470(5)	140 (2) [65]	800 (10) [66]	951±630
	K	-	-	-	11785±9731
	Mg	-	-	-	530±276
	Mn	0.80 (2)	0.768 (31) [67]	0.836±0.500(51) [9]	2.60±2.33
	Na	-	-	-	10211±1432

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

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 ChE 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 thyroid with HT are very limited (Table 2). Results for I and Mn obtained in the present study are some higher than upper limit of published means. Information on Br, Ca, Cl, K, Mg, and Na contents in thyroid with HT was 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 [70,71].

From Table 3, it is observed that in HT samples the mass fraction of Ca and I are approximately two times lower, while the mass fraction of Br is almost 5 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 an auto immune transformation the Br, Ca, and I level in thyroid tissue significantly changed.

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 thyroid with Hashimoto's thyroiditis.

Element	Thyroid tissue				Ratio
	Normal thyroid n=105	Hashimoto's thyroiditis n=8	Student's t-test $p\leq$	U-test p	Hashimoto's thyroiditis to Normal thyroid
Br	16.3±1.3	81.3±22.0	0.097	**≤0.05**	4.99
Ca	1692±109	971±114	**0.0020**	**≤0.01**	0.57
Cl	3400±174	8068±1818	0.234	>0.05	2.37
I	1841±107	951±222	**0.0045**	**≤0.01**	0.52
K	6071±306	11785±5618	0.416	>0.05	1.94
Mg	285±17	530±159	0.264	≤0.05	1.86
Mn	1.35±0.07	2.60±1.35	0.453	>0.05	1.93
Na	6702±1785	10211±827	**0.046**	**≤0.01**	1.52

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

Characteristically, elevated or reduced levels of ChE observed in affected thyroid 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 HT, 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 HT markers.

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

CONCLUSION

In this work, ChE analysis was carried out in the tissue samples of NT and HT 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 observed that in thyroid with HT contents of Br was significantly higher, while Ca and I notably lower than in normal gland. In our opinion, the presented study data strongly suggest that ChE plays an important role in thyroid health, as well asin the etiology and pathogenesis of HT. It was assumed that the differences in ChE levels in affected thyroid tissue could be used as HT markers.

DECLARATION

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.

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