

Comparison of Chemical Element Contents in Thyroid Goiter, Adenoma, and Thyroiditis investigated using Neutron Activation Analysis

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Abstract

Thyroid benign nodules (TBNs) are the most common lesions of this endocrine gland. Among TBNs the colloid goiter (CG), thyroiditis (T), and thyroid adenoma (TA) are the most frequent diseases. An evaluation of the variant of TBNs is clinically important for subsequent therapeutic interventions, as well as for more clear understanding the etiology of these disorders. The aim of this exploratory study was to examine differences in the content of bromine (Br), calcium (Ca), chlorine (Cl), iodine (I), potassium (K), magnesium (Mg), manganese (Mn), and sodium (Na) in tissues of CG, TA, and T. Thyroid tissue levels of eight chemical elements (ChE) were prospectively evaluated in 46 patients with CG, 19 patients with TA, and 12 patients with T. Measurements were performed using non-destructive instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides. Tissue samples were divided into two portions. One was used for morphological study while the other was intended for ChE analysis. It was observed that in CG, TA and T tissues content of Br was significantly higher, while level of I was lower than in normal thyroid tissue. I accumulation in T tissue was lower than in normal thyroid and CG. Abnormal increase in Br level and decrease in I level in all TBNs might demonstrate an involvement of these ChE in etiology and pathogenesis of TBNs. It was suosed that great losses of I in thyroid with T, in contract to little reduced levels of I content in thyroid with CG and TA, could possibly be explored for differential diagnosis of T.

Keywords: Thyroid; Thyroid colloid goiter; Thyroid adenoma; Thyroiditis; Chemical elements; Neutron activation analysis

1. Introduction

Thyroid benign nodules (TBNs) are the most common lesions of this endocrine gland that encountered globally and frequently discovered by palpation during a physical examination, or incidentally, during clinical imaging procedures. TBNs include non-neoplastic lesions (different kinds of thyroid goiter, thyroiditis, and cysts) and neoplastic lesion such as thyroid adenoma. Among TBNs the colloid goiter (CG), thyroiditis (T), and thyroid adenoma (TA) are the most frequent diseases [1-3]. An evaluation of the variant of TBNs is clinically important for subsequent therapeutic interventions. For this reason the finding of specific characteristics of various TBNs is the barest necessity for the differential diagnosis of these thyroid disorders.

For over 20th century, there was the dominant opinion that TBNs is the simple consequence of iodine deficiency. However, it was found that TBNs is a frequent disease even in those countries and regions where the population is never exposed to iodine shortage [4]. Moreover, it was shown that iodine excess has severe consequences on human health and associated with the presence of TBNs [5-8]. It was also demonstrated that besides the iodine deficiency and excess many other dietary, environmental, and occupational factors are associated with the TBNs incidence [9-11]. Among

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these factors a disturbance of evolutionary stable input of many chemical elements (ChE) in human body after industrial revolution plays a significant role in etiology of TBNs [12].

Besides iodine, many other ChE have also essential physiological functions [13]. Essential or toxic (goitrogenic, mutagenic, carcinogenic) properties of ChE depend on tissue-specific need or tolerance, respectively [13]. Excessive accumulation or an imbalance of the ChE may disturb the cell functions and may result in cellular 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 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 investigated in relation to age, gender and some non-thyroidal diseases [23, 24]. After that, variations of many ChE content with age in the thyroid of males and females were studied and age- and gender-dependence of some ChE was observed [25-41]. Furthermore, a significant difference between some ChE contents in CG, TA, and T in comparison with normal thyroid was demonstrated [42-46].

To date, the etiology and pathogenesis of TBNs has to be considered as multifactorial. The present study was performed to find differences in ChE contents between CG, TA, and T group samples, as well as to clarify the role of some ChE in the TBNs etiology. Having this in mind, our aim was to assess the bromine (Br), calcium (Ca), chlorine (Cl), iodine (I), potassium (K), magnesium (Mg), manganese (Mn), and sodium (Na) contents in CG, TA, and T tissue samples 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 CG, TA, and T group samples between each other.

2. Material and methods

All patients suffered from CG (n=46, mean age $M\pm SD$ was 48 ± 12 years, range 30-64), TA (n=19, mean age $M\pm SD$ was 41 ± 11 years, range 22-55), and T (mean age $M\pm SD$ was 39 ± 9 years, range 34-50) were hospitalized in the Head and Neck Department of the Medical Radiological Research Centre. The group of patients with T included 8 persons with Hashimoto's thyroiditis and 6 persons with Riedel's Struma. Thick-needle puncture biopsy of suspicious nodules of the thyroid was performed for every patient, to permit morphological study of thyroid tissue at these sites and to estimate their TE contents. For all patients the diagnosis has been confirmed by clinical and morphological/histological results obtained during studies of biopsy and resected materials.

All tissue samples were divided into two portions using a titanium scalpel [47]. One was used for morphological study while the other was intended for TE analysis. After the samples intended for TE analysis were weighed, they were freeze-dried and homogenized [48]. The powdered samples weighing about 10 mg (for biopsy) and 100 mg (for resected materials) were used for ChE measurement by INAA-SLR.

To determine contents of the ChE by comparison with a known standard, biological synthetic standards (BSS) prepared from phenol-formaldehyde resins were used [49]. In addition to BSS, aliquots of commercial, chemically pure compounds were also used as standards. Ten sub-samples of certified reference material (CRM) of the International Atomic Energy Agency (IAEA) IAEA H-4 (animal muscle) weighing about 100 mg were treated and analyzed in the same conditions as thyroid samples to estimate the precision and accuracy of results.

The content of Br, Ca, Cl, I, K, Mg, Mn, and Na were determined by INAA-SLR using a horizontal channel equipped with the pneumatic rabbit system of the WWR-c research nuclear reactor (Branch of Karpov Institute, Obninsk). Details of used nuclear reactions, radionuclides, gamma-energies, spectrometric unit, sample preparation, and the quality control of results were presented in our earlier publications concerning the INAA-SLR of ChE contents in human thyroid, scalp hair, and prostate [27,28,50-52].

A dedicated computer program for INAA-SLR mode optimization was used [53]. All thyroid samples were prepared in duplicate, and mean values of ChE contents were used in final calculation. Using Microsoft Office Excel software, a summary of the statistics, including, arithmetic mean, and standard deviation, standard error of mean, minimum and maximum values, median, percentiles with 0.025 and 0.975 levels was calculated for ChE contents in CG, TA, and T tissue samples. The difference in the results between three groups of samples (CG, TA, and T) was evaluated by the parametric Student's *t*-test and non-parametric Wilcoxon-Mann-Whitney *U*-test.

3. Results

Table 1 presents certain statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, percentiles with 0.025 and 0.975 levels) of the Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction in CG, TA, and T tissue samples.

The ratios of means and the comparison of mean values of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions in pairs of sample groups such as CG and TA, CG and T, and TA and T are presented in Table 2, 3, and 4, respectively.

Table 5 depicts the results of comparison the contents of Br, Ca, Cl, I, K, Mg, Mn, and Na in CG, TA, and T sample groups with those in normal thyroid [43-46], as well as comparison the contents of these ChE in CG, TA, and T sample groups among themselves.

4. Discussion

As was shown before [27,28,50-52] good agreement of the Br, Ca, Cl, I, K, Mg, Mn, and Na contents in CRM IAEA H-4 samples analyzed by INAA-SLR with the certified data of this CRM indicates acceptable accuracy of the results obtained in the study of CG, TA, and T samples presented in Tables 1–5.

In a general sense variations found for Br, Ca, Cl, I, K, Mg, Mn, and Na contents during the goitrous and adenomatous transformations of thyroid were very similar (Table 2 and 5). The Br, Cl, and Na contents in goitrous and adenomatous thyroid were higher, while I content was lower in comparison with contents of these ChE in normal gland (Table 5). There was not found any differences between ChE contents of CG and TA, with the exception of Br and Mg (Table 2 and 5). The Br level in TA tissue was almost 8 times higher, while the Mg content was 1.8 times lower than in CG tissue.

The variations found for Br, Ca, Cl, I, K, Mg, Mn, and Na in thyroid with T were some differ than the variations of these ChE in CG and TA tissues. Variations of Br and I contents in T samples were similar those in CG and TA tissues, but among other ChE investigated in T samples only Ca content was lower in comparison with normal thyroid (Table 5). The content of Br was higher, whereas the Ca and I levels were lower in T samples than levels of these ChE in CG samples (Table 3 and 5). Only the Mg content was higher, when results for ChE in T samples were compared with those in TA samples (Table 4 and 5).

In this study, content of Cl, K, Mn, and Na in goitrous thyroid were compared with those from adenomatous thyroids and from thyroid with T.

Published data on comparison of Br, Ca, Cl, I, K, Mg, Mn, and Na levels in the different thyroid lesions such as CG, TA and T were not found.

Thus, from obtained results it was possible to conclude that the common characteristics of CG, TA and T samples were elevated level of Br and reduced level of I in comparison with normal thyroid and, therefore, these ChE are involved in etiology or pathogenesis of such thyroid disorders as CG, TA and T.

Br is one of the most abundant and ubiquitous of the recognized ChE in the biosphere. Inorganic bromide is the ionic form of bromine which exerts therapeutic as well as toxic effects. An enhanced intake of bromide could interfere with the metabolism of iodine at the whole-body level. In the thyroid gland the biological behavior of bromide is more similar to the biological behavior of iodide [54]. A significant age-related increase of Br content in human thyroid [25-28] correlated well with age-related prevalence of CG, TA and T [55-57]. The main source of natural Br for human body is food. Environment (air, water and food) polluted by artificial Br-contained compounds, for example such as polybrominated biphenyls (PBBs) and diphenyl ethers (PBDEs), is other source. PBBs and PBDEs impact on thyroid function and thyroid hormones metabolism [58] Thus, on the one hand, the accumulated data suggest that Br level in thyroid tissue might be responsible for CG, TA, and T development. But, on the other hand, Br compounds, especially potassium bromide (KBr), sodium bromide (NaBr), and ammonium bromide (NH₄Br), are frequently used as sedatives in Russia [59]. It may be the reason for elevated levels of Br in specimens of patients with CG, TA and T in comparison with normal thyroid. A nonuniform level of this TE in tissue of thyroid legions TA Br > T Br > CG Br may be explained by the different strength of emotional reactions of persons on the diagnosis Ta, T, and CG, and, as consequence, different doses of Br-contained sedatives, which were used.

Compared to other soft tissues, the human thyroid gland has higher levels of I, because this element plays an important role in its normal functions, through the production of thyroid hormones (thyroxin and triiodothyronine) which are essential for cellular oxidation, growth, reproduction, and the activity of the central and autonomic nervous system. Goitrous and adenomatous transformation, as well as thyroiditis are probably accompanied by a partial loss of tissue-specific functional features, which leads to a modest (CG and TA) or severe (T) reduction in I content associated with functional characteristics of the human thyroid tissue. Great losses of I in thyroid with T, in contract to little reduced levels of I content in thyroid with CG and TA, could possibly be explored for differential diagnosis of T.

Table 1 Some statistical parameters of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in thyroid colloid goiter, adenoma and thyroiditis

Tissue	Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Goiter	Br	36.3	31.3	7.0	8.00	131	26.6	8.95	110
n=46	Ca	1393	855	168	209	4333	1280	258	3219
	Cl	9117	3866	1223	4226	16786	8259	4504	15869
	I	1141	931	145	29	3715	927	106	3617
	K	6518	2304	443	3353	12222	6185	3395	10984
	Mg	351	148	28	13	612	371	45.5	550
	Mn	1.78	1.13	0.23	0.370	5.50	1.70	0.418	4.12
	Na	11335	3597	705	7229	22381	10413	7277	19009
Аденома	Br	286	330	104	3.2	871	133	5.09	841
n=19	Ca	1143	1135	342	52	3582	650	110	3353
	Cl	7722	3785	1262	1757	13824	9085	2043	13179
	I	961	1013	232	131	3906	476	170	3591
	K	5137	2474	686	797	8436	5741	937	8216
	Mg	200	131	36	15.0	397	269	15.0	376
	Mn	1.60	1.77	0.51	0.100	5.54	9.65	0.210	5.08
	Na	9072	3952	1096	2319	16414	9100	2728	15822
Thyroiditis	Br	85	35	13	38.0	125	78	40.6	125
n=14	Ca	694	421	188	111	1169	775	145	1149
	Cl	7160	3541	1771	3499	10487	7328	3594	10442
	I	662	604	161	83.0	1787	356	83.7	1735
	K	7268	1947	974	5690	10111	6635	5759	9852
	Mg	514	232	95	306	844	419	309	835
	Mn	2.33	1.72	0.70	0.570	5.26	2.09	0.615	4.98
	Na	8271	3262	1332	3732	11861	9386	3862	11690

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.

Cl and Na are ubiquitous, extracellular electrolytes essential to more than one metabolic pathway. In the body, Cl and Na mostly present as sodium chloride. Therefore, as usual, there is a correlation between Na and Cl contents in tissues and fluids of human body. Because Cl is halogen like I and Br, in the thyroid gland the biological behavior of chloride has to be similar to the biological behavior of iodide. The main source of natural Cl for human body is salt in food and chlorinated drinking water. Environment (air, water and food) polluted by artificial nonorganic Cl-contained compounds, for example such as sodium chlorate (NaClO_3), and organic Cl-contained compounds, for example such as

polychlorinated biphenyls (PCBs) and dioxin, is other source. There is a clear association between using chlorinated drinking water, levels NaClO_3 , PCBs and dioxin in environment and thyroid disorders, including cancer [58,60-63]. Thus, on the one hand, the accumulated data suggest that Cl level in thyroid tissue might be responsible for CG and TA development. However, on the other hand, it is well known that Cl and Na mass fractions in human tissue samples depend mainly on the extracellular water volume [64]. Goitrous and adenomatous tissues can contain more colloid than normal thyroid. Because colloid is extracellular liquid, it is possible to speculate that CG and TA are characterized by an increase of the mean value of the Cl and Na mass fractions because the relative content of colloid in these thyroid lesions is higher than that in normal thyroid tissue. Overall, the elevated levels of Cl in goitrous and adenomatous thyroids could possibly be explored for diagnosis of CG and TA.

Table 2 Differences between mean values ($M \pm \text{SEM}$) of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in thyroid colloid goiter and adenoma

Element	Thyroid tissue			Ratio	
	Goiter n=46	Аденома n=19	Student's t-test $p \leq$	U-test p	Goiter to Аденома
Br	36.3±7.0	286±104	0.040	≤ 0.01	0.13
Ca	1393±168	1143±342	0.521	>0.05	1.22
Cl	9117±1223	7722±1262	0.438	>0.05	1.18
I	1141±145	961±232	0.518	>0.05	1.19
K	6518±443	5137±686	0.105	>0.05	1.27
Mg	351±28	200±36	0.0030	≤ 0.01	1.76
Mn	1.78±0.23	1.60±0.51	0.741	>0.05	1.11
Na	11335±705	9072±1096	0.096	>0.05	1.25

M - Arithmetic mean, SEM - standard error of mean, statistically significant values are in **bold**.

Table 3 Differences between mean values ($M \pm \text{SEM}$) of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in thyroid colloid goiter and thyroiditis

Element	Thyroid tissue			Ratio	
	Goiter n=46	Thyroiditis n=14	Student's t-test $p \leq$	U-testp	Goiter to Thyroiditis
Br	36.3±7.0	85±13	0.0093	≤ 0.01	0.43
Ca	1393±168	694±188	0.017	≤ 0.01	2.01
Cl	9117±1223	7160±1771	0.397	>0.05	1.27
I	1141±145	662±161	0.034	≤ 0.01	1.72
K	6518±443	7268±974	0.519	>0.05	0.90
Mg	351±28	514±95	0.153	>0.05	0.68
Mn	1.78±0.23	2.33±0.70	0.489	>0.05	0.76
Na	11335±705	8271±1332	0.076	>0.05	1.37

M - Arithmetic mean, SEM - standard error of mean, Statistically significant values are in **bold**

Characteristically, elevated or reduced levels of ChE observed in thyroid nodules are discussed in terms of their potential role in the initiation and promotion of these thyroid lesions. In other words, using the low or high levels of the ChE in affected thyroid tissues researchers try to determine the role of the deficiency or excess of each ChE in the etiology and pathogenesis of thyroid diseases. In our opinion, abnormal levels of many ChE in benign thyroid nodules 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.

This study has several limitations. Firstly, analytical techniques employed in this study measure only eight ChE (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 normal thyroid and in pathologically altered tissue. Secondly, the sample size of CG group particularly of TA and T groups was relatively small and prevented investigations of ChE contents in these groups using differentials like gender, histological types of CG, TA and T, nodules functional activity, stage of disease, dietary habits of patients with CG, TA and T. Lastly, generalization of our results may be limited to Russian population. Despite these limitations, this study provides evidence on TBNs-specific tissue Br, Cl, I, and Na level alteration and shows the necessity to continue ChE research of thyroid benign nodules.

Table 4 Differences between mean values (M±SEM) of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in thyroid adenoma and thyroiditis

Element	Thyroid tissue			Ratio	
	Аденома n=19	Thyroiditis n=14	Student's t-test $p \leq$	U-test p	Аденома to Thyroiditis
Br	286±104	85±13	0.087	>0.05	3.36
Ca	1143±342	694±188	0.270	>0.05	1.65
Cl	7722±1262	7160±1771	0.804	>0.05	1.08
I	961±232	662±161	0.298	>0.05	1.45
K	5137±686	7268±974	0.121	>0.05	0.71
Mg	200±36	514±95	0.019	≤0.01	0.39
Mn	1.60±0.51	2.33±0.70	0.419	>0.05	0.69
Na	9072±1096	8271±1332	0.651	>0.05	1.10

M – Arithmetic mean, SEM – standard error of mean, statistically significant values are in **bold**.

Table 5 Comparison the contents of Br, Ca, Cl, I, K, Mg, Mn, and Na in different pathological transformation of thyroid

Comparison with	Normal thyroid*			Colloid Goiter		Adenoma
	Goiter	Adenoma	Thyroiditis	Adenoma	Thyroiditis	Thyroiditis
Br	↑	↑	↑	↑	↑	=
Ca	=	=	↓	=	↓	=
Cl	↑	↑	=	=	=	=
I	↓	↓	↓	=	↓	=
K	=	=	=	=	=	=
Mg	↑	↑	=	↓	=	↑
Mn	=	=	=	=	=	=
Na	↑	↑	=	=	=	=

* From analysis of previous publications [53, 54], ↑ - element content is higher, ↓ - element content is lower, = - no difference

5. Conclusion

In this work, ChE analysis was carried out in the tissue samples of TBNs 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 specimens. It was observed that in CG, TA and T tissues content of Br was significantly higher, while level of I was lower than in normal thyroid tissue. I accumulation in T tissue was lower than in normal thyroid and CG. In our opinion, the abnormal increase in Br level and decrease in I level in all TBNs might demonstrate an involvement of these ChE in etiology and pathogenesis of TBNs. It was supposed those great losses of I in thyroid with T, in contrast to little reduced levels of I content in thyroid with CG and TA, could possibly be explored for differential diagnosis of T.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declares that he has no competing interests.

Statement of ethical approval

All studies were approved by the Ethical Committees of the Medical Radiological Research Centre (MRRC), Obninsk. 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.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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