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RESEARCH ARTICLE

Differences of Relationships between Iodine and Trace Elements in Normal Thyroid and Thyroid Benign Nodules Revealed by X-Ray Fluorescent Analysis

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ABSTRACT

Thyroid Benign Nodules (TBN) are the most common lesions of this endocrine gland. The etiology of TBN is not clear. The aim of this exploratory study was to examine differences in the content of bromine (Br), cooper (Cu), iron (Fe), iodine (I), rubidium (Rb), strontium (Sr), and zinc (Zn), as well as I/Br, I/Cu, I/Fe, I/Rb, I/Sr, and I/Zn content ratios in tissues of normal thyroid and TBN. Thyroid tissue levels of seven Trace Elements (TEs) were prospectively evaluated in 105 apparently healthy persons and in 79 patients with TBN. Measurements were performed using 109Cd and 241Am radionuclide-induced energy-dispersive X-ray fluorescent analysis. Tissue samples were divided into two portions. One was used for morphological study while the other was intended for TEs analysis. It was observed that in TBN the mass fraction of Br, Cu, and Fe were higher, whereas mass fractions of I as well as I/Br, I/Cu, I/Fe, and I/Zn mass fraction ratios were lower than in normal tissues of the thyroid. These changes can potentially be used as TBN markers. Furthermore, it was found that the levels of Br, Cu, Fe, Rb, Sr, and Zn contents in the normal and affected thyroid gland were interconnected and depend on the content of I in thyroid tissue. Because I plays a decisive role in the function of the thyroid gland, the data obtained allow us to conclude that, along with I, at least such TEs as Br, Cu, Fe, Rb, and Zn, if not directly, then indirectly, are involved in the process of thyroid hormone synthesis.

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Introduction

Thyroid Benign Nodules (TBN) are found in two-thirds of the population, which is a serious clinical and social problem worldwide [1]. TBN includes non-neoplastic lesions (various types of thyroid goiter, thyroiditis, and cysts) and neoplastic lesions such as thyroid adenoma. Among TBN, the most common diseases are colloid goiter, thyroiditis, and thyroid adenoma [2-4]. Throughout the 20th century, the prevailing view was that iodine deficiency was the main cause of TBN. However, numerous studies have shown that TBN is a common disease in those countries and regions where the population has never experienced iodine deficiency [4]. Moreover, an excess intake of iodine has also been found to contribute to the occurrence of TBN [5-8]. It also turned out that,

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along with iodine deficiency and excess, many other dietary, environmental and occupational factors play a role in the etiology of TBN [9-11]. Among these factors, the disruption of the evolutionarily stable intake of many Trace Elements (TEs) into the human body associated with the industrial revolution is a significant importance [12].

In addition to iodine, which is part of thyroid hormones, and selenium, which is involved in thyroid function, other TEs also perform important physiological functions, such as maintaining and regulating cell function, regulating genes, activating or inhibiting enzymatic reactions, and regulating membrane function [13]. The properties of TEs can be essential or toxic (goitrogenic, mutagenic, carcinogenic) depending on specific tissue needs or tolerance, respectively [13]. Excessive accumulation or imbalance of TEs causes dysfunction of cells and leads to cell degeneration, death, benign or malignant transformation [13-15].

For in vivo and in vitro studies of the content of iodine and other TEs in the normal and pathological thyroid gland, we have developed a set of nuclear analytical and related methods [16-22]. Using this set of methods, the influence of age, gender, and some non-endocrine diseases on the level of iodine in the normal human thyroid gland was studied [23,24]. In addition to iodine, the content of many other thyroidal TEs of apparently healthy men and women was determined. As the results of these studies the age [25-35] and gender dependence of some TEs was revealed [36-41]. In addition, it was found that the content of some TEs of the thyroid gland with colloid goiter, thyroiditis and adenoma differs significantly from the levels of these TEs in the normal thyroid gland [42-45].

In studies of the relationship of TEs in the normal thyroid gland, it was shown that the iodine content almost does not correlate with the contents of other TEs. However, the situation changes significantly if, in studies of TEs relationships, not the absolute values of the TEs contents are used, but the relative values of iodine/TEs ratios [46,47].

It is generally accepted that the pathogenesis of TBN is multifactorial. The present study was conducted to elucidate the role of TEs relationship disorders in the pathogenesis of TBN. With this in mind, our aim was to evaluate the content of bromine (Br), copper (Cu), iron (Fe), iodine (I), rubidium (Rb), strontium (Sr), and zinc (Zn) in TBN tissue using Energy Dispersive X-ray Analysis (EDXRF) and calculate individual values of I/TE ratios. TEs such as I, Cu, Fe and Zn play an exceptional role in the normal and pathological physiology of the body in general, and the thyroid gland in particular. EDXRF allows to simultaneously determine all these four TEs, as well as some others. Another aim was to compare the levels of these I/TE ratios in TBN with those in the normal thyroid. Finally, differences in intrathyroidal relationships of I/TE ratios in normal thyroid and TBN was determined.

Material and Methods

The group of patients suffering from TBN (n = 79) included persons with colloid nodular goiter (n = 46), thyroid adenoma (n = 19) and thyroiditis (n = 14). All patients with colloid nodular goiter (mean age M ± SD was 48 ± 12 years, range 30-64 years), thyroid adenoma (mean age M ± SD was 41 ± 11 years, range 22-55 years), and thyroiditis (mean age M ± SD was 39 ± 9 years, range 34-50 years) were hospitalized in the Head and Neck Department of the Medical Radiological Research Center. The group of patients with thyroiditis included 8 persons with Hashimoto's thyroiditis and 6 persons with Riedel's Struma. Each patient underwent a thick-needle puncture biopsy of thyroid nodules for morphological examination and determination of the TEs contents in the obtained material. For all patients the diagnosis was confirmed by clinical and morphological/histological results obtained during studies of biopsy and resected materials.

Normal thyroids for the control group samples were removed at necropsy from 105 deceased (mean age 44 ± 21 years, range 2-87), who had died suddenly. Most of the deaths were caused by trauma incompatible with life. A histological examination in the control group was used to control the age norm conformity, as well as to confirm the absence of micro-nodules and latent cancer.

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.

All samples under study were divided into two portions with a titanium scalpel [48]. One was used for morphological study and the other for TEs analysis. Samples intended for TEs analysis were weighed, lyophilized, and homogenized [49]. The mass fraction of TEs was calculated by the relative way of comparing between intensities of corresponding K_{α}-lines induced by radiation from radionuclide sources in tissue samples and standards. Aliquots of commercial, chemically pure compounds and synthetic standard materials were used as standards [50]. Ten sub-samples of Certified Reference Material (CRM) IAEA H-4 (animal muscle) and IAEA HH-1 (human hair) were analyzed to evaluate the precision and accuracy of the results. The CRM subsamples were prepared in the same manner as dry homogenized thyroid tissue samples.

Detailed information about the EDXRF instruments with ^{109}Cd radionuclide source for determining the content of Br, Cu, Fe, Rb, Sr, Zn and with ^{241}Am radionuclide source for determining the content of I, as well as about methods of analysis and quality control of the results was presented in our earlier publications [21,23-26].

The tissue samples were prepared in duplicate and the average values of the TEs contents were used in the final calculations. Using Microsoft Office Excel software, the main statistical parameters were calculated, including the arithmetic mean, standard deviation, standard error of the mean, minimum and maximum values, median, percentiles with levels of 0.025 and 0.975 for the contents of TEs and I/TEs ratios in normal and TBN. The difference in results between normal and TBN was assessed using the parametric Student's t-test and the non-parametric Wilcoxon-Mann-Whitney U-test. Pearson's correlation coefficient was used in Microsoft Office Excel to calculate the relationship between different TEs contents and between different I/TEs contents ratios in normal thyroid and TBN.

Results

Table 1 depicts comparison of our data for seven TEs in ten sub-samples of CRM IAEA H-4 (animal muscle) and IAEA HH-1 (human hair) with the corresponding certified values of TEs contents in these materials.

Table 2 represents 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, Cu, Fe, I, Rb, Sr, and Zn mass fractions, as well as I/Br, I/Cu, I/Fe, I/Rb, I/Sr, and I/Zn mass fraction ratios in normal thyroid and TBN.

The comparison of our results with published data for the Br, Cu, Fe, I, Rb, Sr, and Zn contents in the human thyroid and TBN is shown in table 3.

Table 4 indicates the differences between mean values of Br, Cu, Fe, I, Rb, Sr, and Zn contents, as well as between mean values of I/Br, I/Cu, I/Fe, I/Rb, I/Sr, and I/Zn mass fraction ratios in normal thyroid and TBN estimated using the parametric Student's t-test and the non-parametric Wilcoxon-Mann-Whitney U-test.

The data of inter-thyroidal correlations (values of *r* – Pearson's coefficient of correlation) between all TEs and between I/TEs ratios identified by us in normal thyroid and TBN are presented in table 5.

Discussion

Precision and accuracy of results

X-ray Fluorescence analysis (XRF) has many implementation options. In addition to EDXRF,

Table 1: EDXRF data of Br, Cu, Fe, I, Rb, Sr, and Zn contents in certified reference material IAEA H-4 (animal muscle) and IAEA HH-1 (human hair) compared to certified values (mg/kg, dry mass basis).

Element	IAEA H-4 Animal Muscle	This Work Results	IAEA HH-1 Human Hair	This Work Results
Br	4.1 ± 1.1[a]	5.0 ± 09	4.2 ± 2.1[b]	3.9 ± 1.6
Cu	4.0 ± 1.0[a]	3.9 ± 1.1	10.2 ± 3.2[a]	-
Fe	49.1 ± 6.5[a]	47.0 ± 1.0	23.7 ± 3.1[a]	25.1 ± 4.3
I	0.08 ± 0.10[b]	< 1.0	20.3 ± 8.9[b]	19.1 ± 6.2
Rb	18.7 ± 3.5[a]	22 ± 4	0.94 ± 0.09[b]	0.89 ± 0.17
Sr	-	< 1	0.82 ± 0.16[b]	1.24 ± 0.57
Zn	86.3 ± 11.5[a]	91 ± 2	174 ± 9[a]	173 ± 17

M: arithmetical mean; SD: Standard Deviation; [a]: certified values; [b]: information values

Table 2: Some statistical parameters of Br, Cu, Fe, I, Rb, Sr, and Zn mass fraction (mg/kg, dry mass basis) as well as I/Br, I/Cu, I/Fe, I/Rb, I/Sr, and I/Zn mass fraction ratios in Normal Thyroid (NT) and Thyroid Benign Nodules (TBN).

Tissue	Element	Mean	SD	SEM	Min	Max	Median	*p* = 0.025	*p* = 0.975
NT	Br	13.9	12.0	1.3	1.4	54.4	10.0	2.23	50.8
n = 105	Cu	4.23	1.52	0.18	0.50	7.50	4.15	1.57	7.27
	Fe	222	102	11	47.1	512	204	65.7	458
	I	1622	1036	107	110	5150	1505	220	3927
	Rb	9.03	6.17	0.66	1.80	42.9	7.81	2.48	25.5
	Sr	4.55	3.22	0.37	0.10	13.7	3.70	0.48	12.3
	Zn	112	44.0	4.7	6.10	221	106	35.5	188
	I/Br	192	172	19	3.94	902	136	5.10	622
	I/Cu	454	472	59	18.6	2756	330	32.6	1716
	I/Fe	10.9	11.9	1.37	0.223	59.4	6.27	0.808	41.9
	I/Rb	243	228	26	11.1	1036	171	25.4	816
	I/Sr	953	2225	276	13.2	16570	350	37.1	4345
	I/Zn	19.2	26.6	3.0	0.679	222	14.6	1.44	47.0
TBN	Br	412	682	98	3.20	2628	64.5	8.35	2336
n = 79	Cu	10.2	9.2	1.7	2.90	35.2	6.0	3.04	34.9
	Fe	345	416	49	52,0	2563	185	54.3	1435
	I	1107	1358	154	47.0	8260	702	84.9	3880
	Rb	8.77	4.49	0.53	1.00	20.3	8.30	1.18	18.8
	Sr	4.48	6.84	0.88	0.42	32.0	1.90	0.769	27.5
	Zn	112.9	51.4	6.1	22.0	270	100	47.8	239
	I/Br	28.7	66.3	9.6	0.103	374	5.82	0.303	243
	I/Cu	244	315	60	6.69	1400	113	14.9	1036
	I/Fe	7.48	11.4	1.4	0.25	80.2	3.16	0.27	27.5
	I/Rb	212	285	34	3.51	1336	109	4.82	1120
	I/Sr	652	805	105	6.85	3591	239	16.6	2584
	I/Zn	12.2	14.8	1.77	0.55	74.6	7.16	1.29	57.8

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

there is a variant of Wave Dispersion (WDXRF), Total Reflection (TXRF), while the radiation of radionuclides, an X-ray tube, and even a synchrotron can be used to excite the characteristic X-ray radiation of atoms. The WDXRF in multi-elemental analysis takes much more time than the EDXRF. The variant of TXRF is a destructive method, i.e. requires acid digestion of the sample. We chose the cheapest version of the EDXRF device, which allowed us to quickly determine the contents of all the TEs under study without destroying the sample investigated.

Good agreement of the Br, Cu, Fe, I, Rb, Sr, and Zn contents analyzed by EDXRF with the certified data of CRMs IAEA H-4 and IAEA HH-1 (Table 1) indicates an acceptable accuracy of the results obtained in the study for TEs contents and I/TEs content ratios in the normal thyroid and TBN presented in tables 2-5.

The contents of TEs was determined in all or most of the examined samples, which made it possible to calculate the main statistical parameters: the mean value of the Mass fraction (M), Standard Deviation (SD), Standard Error of the Mean (SEM), Minimum (Min), Maximum (Max), Median (Med), and percentiles with levels of 0.025 ($p = 0.025$) and 0.975 ($p = 0.975$), of the Br, Cu, Fe, I, Rb, Sr, and Zn mass fractions, as well as I/Br, I/Cu, I/Fe, I/Rb, I/Sr, and I/Zn mass fraction ratios in normal thyroid and TBN (Table 2). The values of M, SD, and SEM can be used to compare data for normal thyroid and TBN only under the condition of a normal distribution of the results of determining the content of TEs in the samples under study. Statistically reliable identification of the law of distribution of results requires large sample sizes, usually several hundred samples, and therefore is rarely used in biomedical research. In the conducted

Table 3: Median, minimum and maximum value of means Br, Cu, Fe, I, Rb, Sr, and Zn contents in normal thyroid and Thyroid Benign Nodules (TBN) 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) [51]	284 ± 44 (14) [52]	13.9 ± 12.0
	Cu	6.1 (57)	1.42 (120) [53]	220 ± 22 (10) [54]	4.23 ± 1.52
	Fe	252 (21)	56 (120) [53]	2444 ± 700 (14) [52]	222 ± 102
	I	1888 (95)	159 ± 8 (23) [55]	5772 ± 2708 (50) [56]	1618 ± 1041
	Rb	12.3 (9)	≤ 0.85 (29) [57]	294 ± 191 (14) [52]	9.03 ± 6.17
	Sr	0.73 (9)	0.55 ± 0.26 (21) [58]	46.8 ± 4.8 (4) [54]	4.55 ± 3.22
	Zn	118 (51)	32 (120) [53]	820 ± 204 (14) [52]	112 ± 44
TBN	Br	585 (5)	20.2 ± 11.3 (5) [59]	1277 (1) [60]	412 ± 682
	Cu	13.4 (6)	2.8 ± 0.8 (13) [61]	120 ± 52 (11) [52]	10.2 ± 9.2
	Fe	296 (7)	54.6 ± 36.1 (5) [59]	4848 ± 3056 (11) [52]	345 ± 416
	I	640 (13)	77 ± 14 (66) [62]	2720 ± 1228 (12) [63]	1107 ± 1358
	Rb	7.5 (2)	7.0 (10) [64]	864 ± 148 (11) [52]	8.77 ± 4.49
	Sr	14 (2)	1.64 ± 1.44 (51) [65]	27.2 ± 2.4 (4) [54]	4.48 ± 6.84
	Zn	160 (11)	60 ± 24 (13) [61]	1236 ± 560 (2) [66]	113 ± 51

M: arithmetic mean; SD: Standard Deviation: (n)*: number of all references; (n)**: number of samples

Table 4: Differences between mean values (M ± SEM) of Br, Cu, Fe, Rb, Sr, and Zn mass fraction (mg/kg, dry mass basis), as well as I/Br, I/Cu, I/Fe, I/Rb, I/Sr, and I/Zn mass fraction ratios in Normal Thyroid (NT) and Thyroid Benign Nodules (TBN).

Element Ratio	Thyroid Tissue				Ratio
	NT	TBN	Student's t-test, $p \leq$	U-test, p	TBN/NT
Br	13.9 ± 1.3	412 ± 98	0.0002*	< 0.01*	29.6
Cu	4.23 ± 0.18	10.2 ± 1.7	0.0018*	< 0.01*	2.41
Fe	222 ± 11	345 ± 49	0.018*	< 0.01*	1.55
I	1618 ± 108	1107 ± 154	0.007*	< 0.01*	0.68
Rb	9.03 ± 0.66	8.77 ± 0.53	0.757	> 0.05	0.97
Sr	4.55 ± 0.37	4.48 ± 0.88	0.948	> 0.05	0.98
Zn	112 ± 5	113 ± 6	0.944	> 0.05	1.00
I/Br	191 ± 19	28.7 ± 9.6	< 0.00001*	< 0.01*	0.15
I/Cu	454 ± 59	244 ± 60	0.015*	< 0.01*	0.54
I/Fe	10.9 ± 1.4	7.5 ± 1.4	0.079	< 0.05*	0.69
I/Rb	243 ± 26	212 ± 34	0.472	> 0.05	0.87
I/Sr	953 ± 276	652 ± 105	0.310	> 0.05	0.68
I/Zn	19.2 ± 3.0	12.2 ± 1.8	0.048*	< 0.05*	0.64

M: arithmetic mean; SEM: Standard Error of Mean; *: Significant values

study, we could not prove or disprove the "normality" of the distribution of the results obtained due to the insufficient number of samples studied. Therefore, in addition to the M, SD, and SEM values, such statistical characteristics as Median, range (Min-Max) and percentiles $p = 0.025$ and $p = 0.975$ were calculated, which are valid for any law of distribution of the results of TEs contents in normal and pathological thyroid tissue.

Comparison with published data

The obtained means for Br, Cu, Fe, Rb, Sr, and Zn mass fraction, as shown in table 3, agree well with the medians of mean values cited by other researches for the human thyroid, including samples received from persons who died from different non-thyroid diseases [51-58]. Our means for Br, Cu, Fe, Rb, Sr, and Zn mass fraction in TBN (Table 3) are also within the range of published mean values for these TEs and agree well with their medians [59-66]. Some values for means of TEs mass fractions reported were not expressed on a dry mass basis. Because of this we recalculated these values using published data for water (75%) [67] and ash (4.16% on dry mass basis) [68] contents in thyroid of adults.

No published data referring I/Br, I/Cu, I/Fe, I/Rb, I/Sr, I/Zn in the normal thyroid gland and TBN were found.

The results shown in table 3 for the normal thyroid also includes samples from patients who died from various non-endocrine diseases. In our previous study, it was shown that some non-endocrine diseases can affect the contents of TEs in the thyroid gland [24]. Moreover, in many studies, "normal" thyroid refers to visually unaffected tissue adjacent to benign or malignant thyroid nodules. However, it was previously found that the tissue adjacent to benign or malignant thyroid nodules is not identical in its elemental composition to healthy thyroid tissue [69-74].

The range of means of Br, Cu, Fe, I, Rb, Sr, and Zn reported in the literature for normal thyroid and TBN vary widely (Table 3). This can be explained by the dependence of the TEs content on many factors, including the “normality” of the thyroid samples (see above), the region of the thyroid gland from which the sample was taken, age, gender, ethnicity, gland mass, and goiter stage. Not all these factors were strictly controlled in the cited studies. However, in our opinion, the main reasons for the variability in published data may be related to the accuracy of analytical methods, sample preparation methods, and the impossibility of taking homogeneous samples from affected tissues. It was insufficient quality control of results in these studies. In many scientific investigations, tissue samples were incinerated 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, significant amounts of some TEs are lost as a result of such processing. This applies not only to such volatile halogens as Br and I, but also to other TEs studied in the present work [75-77].

Differences between the normal thyroid and TBN in the contents of TEs and I/TEs relationships

From table 4, it is observed that in TBN the mass fraction of Br, Cu, and Fe were 29.6, 2.41, and 1.55 times higher, respectively, whereas mass fractions of I was 32% lower than in normal tissues of the thyroid. Since the changes in the content of Br, Cu, and Fe, on the one hand, and I, on the other hand, in TBN were in different directions, the ratios of I/Br, I/Cu, and I/Fe in TBN also differed significantly from the norm (Table 4). Moreover, the I/Zn ratio in TBN was significantly below (36%) the normal level. This confirmed that the I/TEs ratios are more sensitive parameters than the absolute values of the TEs contents in thyroid tissue.

Generally, elevated or decreased levels of TEs observed in TBN are discussed in terms of their potential role in the pathogenesis of TBN. In other words, researchers are trying to determine the role of deficiency or excess of each TEs in the occurrence of TBN by the low or high levels of TEs in TBN tissues. In our opinion, the abnormal levels of many TEs in TBN could be both a cause and a consequence of thyroid transformation. Thus, based on the results of such studies, it is not possible to decide whether the measured decrease or increase in the levels of TEs in pathologically altered tissue is the cause or consequence of the disease.

Relationships between trace elements in normal thyroid and TBN

A significant direct correlation between the mass fractions of Cu and Fe, as well as an inverse correlation between the mass fractions of I and Fe, was observed in the normal thyroid gland (Table 5). The absence of correlations between I and other TEs in the normal thyroid gland, with the exception of an inverse relationship between I and Fe, suggested that the content of Br, Cu, Rb, Sr, and Zn in the thyroid gland does not depend on the content of iodine. However, this is not quite true. When the contents of the studied TEs was reduced to the content of I (I/TEs ratios), it turned out that there are several significant direct correlations between I/Br, I/Cu, I/Fe, I/Rb, I/Sr, and I/Zn (Table 5).

In TBN, there were no correlations between Cu and Fe and between I and Fe, as well as an inverse correlation between the mass fractions of I and Fe, but new direct relationships between Br and Zn and between Cu and Sr appeared. As for the I/TEs ratios in TBN, all studied ratios (I/Br, I/Cu, I/Fe, I/Rb, I/Sr

Table 5: Intercorrelations of the trace element mass fraction and the I/trace element mass fraction ratios in the normal thyroid and Thyroid Benign Nodules (TBN) (*r* - coefficient of correlation).

Thyroid	Element	Br	Cu	Fe	I	Rb	Sr	Zn
Normal	Br	**1.00**	0.23	0.15	0.05	0.13	0.19	0.12
	Cu	0.23	**1.00**	0.32[b]	-0.17	0.23	-0.05	0.16
	Fe	0.15	0.32[b]	**1.00**	-0.32[b]	0.18	-0.02	0.14
	I	0.05	-0.17	-0.32[b]	**1.00**	-0.07	-0.20	0.06
	Rb	0.13	0.23	0.18	-0.07	**1.00**	0.09	0.22
	Sr	0.19	-0.05	-0.02	-0.20	0.09	**1.00**	0.12
	Ratio	I/Br	I/Cu	I/Fe	I/Rb	I/Sr	I/Zn	
	I/Br	**1.00**	0.29[a]	0.39[c]	0.39[c]	0.25	0.05	
	I/Cu	0.29[a]	**1.00**	0.50[b]	0.57[c]	0.13	0.74[c]	
	I/Fe	0.39[c]	0.50[b]	**1.00**	0.61[c]	0.19	0.24[a]	
	I/Rb	0.39[c]	0.57[c]	0.61[c]	**1.00**	0.11	0.31[b]	
	I/Sr	0.25	0.13	0.19	0.11	**1.00**	0.04	
	I/Zn	0.05	0.74[c]	0.24[a]	0.31[b]	0.04	**1.00**	
	Zn	0.12	0.16	0.14	0.06	0.22[a]	0.12	**1.00**
	Element	Br	Cu	Fe	I	Rb	Sr	Zn
TBN	Br	**1.00**	0.08	-0.15	0.04	0.13	-0.09	0.41[b]
	Cu	0.08	**1.00**	0.27	-0.15	0.09	0.36[a]	0.06
	Fe	-0.15	0.27	**1.00**	0.01	0.01	0.05	0.03
	I	0.04	-0.15	0.01	**1.00**	-0.21	0.05	0.10
	Rb	0.13	0.09	0.01	-0.21	**1.00**	-0.16	-0.10
	Sr	-0.09	0.36[a]	0.05	0.05	-0.16	**1.00**	-0.14
	Zn	0.41[b]	0.06	0.03	0.10	-0.10	-0.14	**1.00**
	Ratio	I/Br	I/Cu	I/Fe	I/Rb	I/Sr	I/Zn	
	I/Br	**1.00**	0.74[c]	0.44[c]	0.67[c]	0.02	0.83[c]	
	I/Cu	0.74[c]	**1.00**	0.79[c]	0.73[c]	0.76[c]	0.84[c]	
	I/Fe	0.44[c]	0.79[c]	**1.00**	0.60[c]	0.65[c]	0.52[c]	
	I/Rb	0.67[c]	0.73[c]	0.60[c]	**1.00**	0.40[b]	0.84[c]	
	I/Sr	0.02	0.76[c]	0.65[c]	0.40[b]	**1.00**	0.45[c]	
	I/Zn	0.83[c]	0.84[c]	0.52[c]	0.84[c]	0.45[c]	**1.00**	

Significant values: [a] < 0.05, [b] < 0.01, [c] < 0.001

and I/Zn) were directly correlated with each other, except for I/Br and I/Sr (Table 5). It followed that, at least, the levels of Br, Cu, Fe, Rb, and Zn in the normal thyroid gland and TBN are interrelated and depend on the content of I in it and that along with I these TEs participate, if not directly, then indirectly, in the process of synthesis of thyroid hormones.

Conclusion

The ^{109}Cd and ^{241}Am radionuclide-induced EDXRF is a useful analytical tool for the non-destructive determination of TEs contents in the normal and affected thyroid tissue samples. This method allows determine means for Br, Cu, Fe, I, Rb, Sr, and Zn (seven TEs).

Our data reveal that in TBN the mass fraction of Br, Cu, and Fe were higher, whereas mass fractions of I as well as I/Br, I/Cu, I/Fe, and I/Zn mass fraction ratios were lower than in normal tissues of the thyroid. These changes can potentially be used as TBN markers. Furthermore, it was found that the levels of Br, Cu, Fe, Rb, Sr, and Zn contents in the normal and affected thyroid gland were interconnected and depend on the content of I in thyroid tissue. Because I plays a decisive role in the function of the thyroid gland, the data obtained allow us to conclude that, along with I, at least such TEs as Br, Cu, Fe, Rb, and Zn, if not directly, then indirectly, are involved in the process of thyroid hormone synthesis. It follows that for the normal functioning of the thyroid gland, it is necessary to maintain an adequate concentration of I in its tissue, balanced with the levels of other TEs.

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Conflict of Interest

The author has not declared any conflict of interests.

References

1. Kassi GN, Evangelopoulou CC, Papapostolou KD, Karga HJ. Benign and malignant thyroid nodules with autoimmune thyroiditis. Arch Endocrinol Metab. 2022 Sept 08;66(4):446-451. doi: 10.20945/2359-3997000000483. Epub 2022 Jun 2. PMID: 35657125.
2. Ghartimagar D, Ghosh A, Shrestha MK, Thapa S, Talwar OP. Histopathological Spectrum of Non-Neoplastic and Neoplastic Lesions of Thyroid: A Descriptive Cross-sectional Study. JNMA J Nepal Med Assoc. 2020 Nov 22;58(231):856-861. doi: 10.31729/jnma.5038. PMID: 34506431; PMCID: PMC7775000.
3. Hoang VT, Trinh CT. A Review of the Pathology, Diagnosis and Management of Colloid Goitre. Eur Endocrinol. 2020 Oct;16(2):131-135. doi: 10.17925/EE.2020.16.2.131. Epub 2020 Oct 6. PMID: 33117444; PMCID: PMC7572169.
4. Popoveniuc G, Jonklaas J. Thyroid nodules. Med Clin North Am. 2012 Mar;96(2):329-49. doi: 10.1016/j.mcna.2012.02.002. PMID: 22443979; PMCID: PMC3575959.
5. Zaichick V. Iodine excess and thyroid cancer. J Trace Elem Exp Med. 1998;11(4):508-509.
6. Zaichick V, Iljina T. Dietary iodine supplementation effect on the rat thyroid ^{131}I blastomogenic action. In: Die Bedentung der Mengen- und Spurenelemente. 18. Arbeitstangung. Friedrich-Schiller-Universität, Jena. 1998. p.294-306.
7. Kim S, Kwon YS, Kim JY, Hong KH, Park YK. Association between Iodine Nutrition Status and Thyroid Disease-Related Hormone in Korean Adults: Korean National Health and Nutrition Examination Survey VI (2013-2015). Nutrients. 2019 Nov 13;11(11):2757. doi: 10.3390/nu11112757. PMID: 31766270; PMCID: PMC6893705.
8. Vargas-Uricoechea H, Pinzón-Fernández MV, Bastidas-Sánchez BE, Jojoa-Tobar E, Ramírez-Bejarano LE, Murillo-Palacios J. Iodine Status in the Colombian Population and the Impact of Universal Salt Iodization: A Double-Edged Sword? J Nutr Metab. 2019 Apr 1;2019:6239243. doi: 10.1155/2019/6239243. PMID: 31061736; PMCID: PMC6466914.
9. Stojsavljević A, Rovčanin B, Krstić D, Borković-Mitić S, Paunović I, Diklić A, Gavrović-Jankulović M, Manojlović D. Risk assessment of toxic and essential trace metals on the thyroid health at the tissue level: The significance of lead and selenium for colloid goiter disease. Expo Health. 2019. doi: 10.1007/s12403-019-00309-9.
10. Fahim YA, Sharaf NE, Hasani IW, Ragab EA, Abdelhakim HK. Assessment of Thyroid Function and Oxidative Stress State in Foundry Workers Exposed to Lead. J Health Pollut. 2020 Aug 19;10(27):200903. doi: 10.5696/2156-9614-10.27.200903. PMID: 32874759; PMCID: PMC7453815.
11. Liu M, Song J, Jiang Y, Liu Y, Peng J, Liang H, Wang C, Jiang J, Liu X, Wei W, Peng J, Liu S, Li Y, Xu N, Zhou D, Zhang Q, Zhang J. A case-control study on the association of mineral elements exposure and thyroid tumor and goiter. Ecotoxicol Environ Saf. 2021 Jan 15;208:111615. doi: 10.1016/j.ecoenv.2020.111615. Epub 2020 Nov 12. PMID: 33396135.
12. Zaichick V. Medical elementology as a new scientific discipline. J Radioanal Nucl Chem. 2006;269:303-309. doi: 10.1007/s10967-006-0383-3.
13. Moncayo R, Moncayo H. A post-publication analysis of the idealized upper reference value of 2.5 mIU/L for TSH: Time to support the thyroid axis with magnesium and iron especially in the setting of reproduction medicine. BBA Clin. 2017 Mar 19;7:115-119. doi: 10.1016/j.bbacli.2017.03.003. PMID: 28409122; PMCID: PMC5385584.
14. Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. Arch Toxicol. 2008 Aug;82(8):493-512. doi: 10.1007/s00204-008-0313-y. Epub 2008 May 22. PMID: 18496671.
15. Martinez-Zamudio R, Ha HC. Environmental epigenetics in metal exposure. Epigenetics. 2011 Jul;6(7):820-7. doi: 10.4161/epi.6.7.16250. Epub 2011 Jul 1. PMID: 21610324; PMCID: PMC3230540.
16. Zaĭchik VE, Raibukhin IuS, Mel'nik AD, Cherkashin VI. Neĭtron-aktivatsionnyĭ analiz v izuchenii povedeniia ĭoda v organizme [Neutron-activation analysis in the study of the behavior of iodine in the organism]. Med Radiol (Mosk). 1970 Jan;15(1):33-6. Russian. PMID: 5449249.
17. Zaĭchik VE, Matveenko EG, Vtiurin BM, Medvedev VS. Intratireoidnyĭ ĭod v diagnostike raka shchitvidnoĭ zhelezy [Intrathyroid iodine in the diagnosis of thyroid cancer]. Vopr Onkol. 1982;28(3):18-24. Russian. PMID: 7064415.
18. Zaichick VYe, Tsyb AF, Vtyurin BM. Trace elements and thyroid cancer. Analyst. 1995 Mar;120(3):817-21. doi: 10.1039/an9952000817. PMID: 7741233.
19. Zaichick V Ye, Choporov Yu Ya. Determination of the natural level of human intra-thyroid iodine by instrumental neutron

activation analysis. J Radioanal Nucl Chem. 1996;207(1):153-161. doi: 10.1007/BF02036535.

20. Zaichick V. *In vivo* and *in vitro* application of energy-dispersive XRF in clinical investigations: Experience and the future. J Trace Elem Exp Med. 1998;11(4):509-510.

21. Zaichick V, Zaichick S. Energy-dispersive X-ray fluorescence of iodine in thyroid puncture biopsy specimens. J Trace Microprobe Tech. 1999;17(2):219-232.

22. Zaichick V. Relevance of, and potentiality for, in vivo intrathyroidal iodine determination. Ann N Y Acad Sci. 2000 May;904:630-1. doi: 10.1111/j.1749-6632.2000.tb06530.x. PMID: 10865819.

23. Zaichick V, Zaichick S. Normal human intrathyroidal iodine. Sci Total Environ. 1997 Oct 27;206(1):39-56. doi: 10.1016/s0048-9697(97)00215-5. PMID: 9373990.

24. Zaichick V. Human intrathyroidal iodine in health and non-thyroidal disease. In: New aspects of trace element research. Abdulla M, Bost M, Gamon S, Arnaud P, Chazot G, editors. Smith-Gordon, London, and Nishimura, Tokyo: 1999. p.114-119.

25. Zaichick V, Zaichick S. Age-related changes of some trace element contents in intact thyroid of females investigated by energy dispersive X-ray fluorescent analysis. Trends Geriatr Health. 2017;1(1):31-38.

26. Zaichick V, Zaichick S. Age-related changes of some trace element contents in intact thyroid of males investigated by energy dispersive X-ray fluorescent analysis. MOJ Gerontol Ger. 2017;1(5):00028.

27. Zaichick V, Zaichick S. Age-related changes of Br, Ca, Cl, I, K, Mg, Mn, and Na contents in intact thyroid of females investigated by neutron activation analysis. Curr Updates Aging. 2017;015.

28. Zaichick V, Zaichick S. Age-related changes of Br, Ca, Cl, I, K, Mg, Mn, and Na contents in intact thyroid of males investigated by neutron activation analysis. J Aging Age Relat Dis. 2017;1(1):1002.

29. Zaichick V, Zaichick S. Age-related changes of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn contents in intact thyroid of females investigated by neutron activation analysis. J Gerontol Geriatr Med. 2017;3:015.

30. Zaichick V, Zaichick S. Age-related changes of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn contents in intact thyroid of males investigated by neutron activation analysis. Curr Trends Biomedical Eng Bio sci. 2017;4(4):555644. doi: 10.19080/CTBEB.2017.04.555644.

31. Zaichick V, Zaichick S. Effect of age on chemical element contents in female thyroid investigated by some nuclear analytical methods. MicroMedicine. 2018;6(1):47-61.

32. Zaichick V, Zaichick S. Neutron activation and X-ray fluorescent analysis in study of association between age and chemical element contents in thyroid of males. Op Acc J Bio Eng Bio Sci. 2018;2(4):202-212. doi: 10.32474/OAJBEB.2018.02.000144.

33. Zaichick V, Zaichick S. Variation with age of chemical element contents in females' thyroids investigated by neutron activation analysis and inductively coupled plasma atomic emission spectrometry. J Biochem Analyt Stud. 2018;3(1):1-10. doi: 10.16966/2576-5833.114.

34. Zaichick V, Zaichick S. Association between age and twenty chemical element contents in intact thyroid of males. SM Gerontol Geriatr Res. 2018;2(1):1014.

35. Zaichick V, Zaichick S. Associations between age and 50 trace element contents and relationships in intact thyroid of males. Aging Clin Exp Res. 2018 Sep;30(9):1059-1070. doi: 10.1007/s40520-018-0906-0. Epub 2018 Feb 2. PMID: 29396842.

36. Zaichick V, Zaichick S. Possible role of inadequate quantities of intra-thyroidal bromine, rubidium and zinc in the etiology of female subclinical hypothyroidism. EC Gynaecology. 2018;7(3):107-115.

37. Zaichick V, Zaichick S. Possible role of inadequate quantities of intra-thyroidal bromine, calcium and magnesium in the etiology of female subclinical hypothyroidism. Int Gyn and Women's Health. 2018;1(3). doi: 10.32474/IGWHC.2018.01.000113.

38. Zaichick V, Zaichick S. Possible role of inadequate quantities of intra-thyroidal cobalt, rubidium and zinc in the etiology of female subclinical hypothyroidism. Womens Health Sci J. 2018;2(1):000108. doi: 10.23880/whsj-16000108.

39. Zaichick V, Zaichick S. Association between female subclinical hypothyroidism and inadequate quantities of some intra-thyroidal chemical elements investigated by X-ray fluorescence and neutron activation analysis. Gynaecology and Perinatology. 2018;2(4):340-355.

40. Zaichick V, Zaichick S. Investigation of association between the high risk of female subclinical hypothyroidism and inadequate quantities of twenty intra-thyroidal chemical elements. Clin Res: Gynecol Obstet. 2018;1(1):1-18.

41. Zaichick V, Zaichick S. Investigation of association between the high risk of female subclinical hypothyroidism and inadequate quantities of intra-thyroidal trace elements using neutron activation and inductively coupled plasma mass spectrometry. Acta Scientific Medical Sciences. 2018;2(9):23-37.

42. Zaichick V. Comparison of trace element contents in thyroid goiter, adenoma, and thyroiditis investigated using X-ray fluorescent analysis. Oncology and Cancer Screening. 2021;4(1):1-7.

43. Zaichick V. Comparison of chemical element contents in thyroid goiter, adenoma, and thyroiditis investigated using neutron activation analysis. World Journal of Advanced Research and Reviews. 2021;12(3):98-107. doi: 10.30574/wjarr.2021.12.3.0656.

44. Zaichick V. Comparison of ten trace element contents in thyroid goiter, adenoma, and thyroiditis investigated using neutron activation analysis. Journal of Clinical Research in Oncology. 2022;4(2):1-9. doi: 10.33309/2639-8230.040201.

45. Zaichick V. Comparison of chemical element contents in

thyroid goiter, adenoma, and thyroiditis investigated using X-ray fluorescence and neutron activation analysis. Saudi Journal of Biomedical Research. 2021;6(12):268-279. doi: 10.36348/sjbr.2021.v06i12.001.

46. Zaichick V. Relationships between iodine and some trace elements in normal thyroid of females investigated by energy dispersive X-ray fluorescent analysis. **Women's Health Science Journal. 2023;7(1):1-8. doi:** 10.23880/whsj-16000171**.**

47. Zaichick V. Relationships between iodine and some trace elements in normal thyroid of males investigated by energy dispersive X-ray fluorescent analysis. Journal of Clinical Oncology Reports. 2023;2(1):1-9.

48. Zaichick V, Zaichick S. Instrumental effect on the contamination of biomedical samples in the course of sampling. The Journal of Analytical Chemistry. 1996;51(12):1200-1205.

49. Zaichick V, Tsislyak YuV. A simple device for biosample lyophilic drying. Lab Delo. 1978;2:109-110.

50. Zaichick V. Applications of synthetic reference materials in the medical Radiological Research Centre. Fresenius J Anal Chem. 1995;352:219-223.

51. Zhu H, Wang N, Zhang Y, Wu Q, Chen R, Gao J, Chang P, Liu Q, Fan T, Li J, Wang J, Wang J. Element contents in organs and tissues of Chinese adult men. Health Phys. 2010 Jan;98(1):61-73. doi: 10.1097/HP.0b013e3181bad921. PMID: 19959952.

52. Salimi J, Moosavi K, Vatankhah S, Yaghoobi A. Investigation of heavy trace elements in neoplastic and non-neoplastic human thyroid tissue: A study by proton induced X-ray emissions. Iran J Radiat Res. 2004;1(4):211-216.

53. Ataullakhanov IA. Vozrastnye izmeneniia v soderzhanii margantsa, kobal'ta, medi, tsinka i zheleza zhelezakh vnutrenneĭ sekretsii zhenshchin [Age changes in the content of manganese, cobalt, copper, zinc and iron in the endocrine glands of women]. Probl Endokrinol (Mosk). 1969 Mar-Apr;15(2):98-102. Russian. PMID: 5807109.

54. Reddy SB, Charles MJ, Kumar MR, Reddy BS, Anjaneyulu Ch, Raju GJN, Sundareswar B, Vijayan V. Trace elemental analysis of adenoma and carcinoma thyroid by PIXE method. Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms. 2002;196(3-4):333-339. doi: 10.1016/S0168-583X(02)01292-2.

55. Neĭmark II, Timoshnikov VM. O razvitii raka shchitovidnoĭ zhelezy u lits, prozhivaiushchikh v ochage zobnoĭ endemii [Development of thyroid cancer in persons living in the endemic goiter area]. Probl Endokrinol (Mosk). 1978 May-Jun;24(3):28-32. Russian. PMID: 674124.

56. Zabala J, Carrión N, Murillo M, Quintana M, Chirinos J, Seijas N, Duarte L, Brätter P. Determination of normal human intrathyroidal iodine in Caracas population. J Trace Elem Med Biol. 2009;23(1):9-14. doi: 10.1016/j.jtemb.2008.11.002. Epub 2009 Jan 23. PMID: 19203711.

57. Boulyga SF, Zhuk IV, Lomonosova EM, Kanash NV, Bazhanova NN. Determination of microelements in thyroids of the inhabitants of Belarus by neutron activation analysis using the k_0-method. J Radioanal Nucl Chem. 1997;222(1-2):11-14. doi: 10.1007/BF02034238.

58. TIPTON IH, COOK MJ. Trace elements in human tissue. II. Adult subjects from the United States. Health Phys. 1963 Feb;9:103-45. doi: 10.1097/00004032-196302000-00002. PMID: 13985137.

59. Maeda K, Yokode Y, Sasa Y, Kusuyama H, Uda M. Multielemental analysis of human thyroid glands using Particle Induced X-ray Emission (PIXE)**.** Nucl Instrum Methods Phys Res B. 1987;22(1-3):188-190. doi: 10.1016/0168-583X(87)90323-5.

60. TURETSKAIA ES. [Studies on goitrous thyroid glands for iodine and bromine content]. Probl Endokrinol Gormonoter. 1961 Mar-Apr;7:75-80. Russian. PMID: 13778682.

61. Yaman M, Akdeniz I. Sensitivity enhancement in flame atomic absorption spectrometry for determination of copper in human thyroid tissues. Anal Sci. 2004 Sep;20(9):1363-6. doi: 10.2116/analsci.20.1363. PMID: 15478350.

62. Błażewicz A, Orlicz-Szczęsna G, Szczęsny P, Prystupa A, Grzywa-Celińska A, Trojnar M. A comparative analytical assessment of iodides in healthy and pathological human thyroids based on IC-PAD method preceded by microwave digestion. J Chromatogr B Analyt Technol Biomed Life Sci. 2011 Mar 15;879(9-10):573-8. doi: 10.1016/j.jchromb.2011.01.008. Epub 2011 Jan 14. PMID: 21330222.

63. LeBlanc AD, Bell RL, Johnson PC. Measurement of 127I concentration in thyroid tissue by x-ray fluorescence. J Nucl Med. 1973 Nov;14(11):816-9. PMID: 4743035.

64. Kvícala J, Havelka J, Němec J, Zeman V. Selenium and rubidium changes in subjects with pathologically altered thyroid. Biol Trace Elem Res. 1992 Jan-Mar;32:253-8. doi: 10.1007/BF02784608. PMID: 1375062.

65. Antonova MV, Elinova VG, Voitekhovskaya YaV. Some trace element contents in thyroid and water in endemic goiter region. Zdravookhranenie BSSR. 1966;9:42-44.

66. Zagrodzki P, Nicol F, Arthur JR, Słowiaczek M, Walas S, Mrowiec H, Wietecha-Posłuszny R. Selenoenzymes, laboratory parameters, and trace elements in different types of thyroid tumor. Biol Trace Elem Res. 2010 Apr;134(1):25-40. doi: 10.1007/s12011-009-8454-2. Epub 2009 Jul 14. PMID: 19597722.

67. Katoh Y, Sato T, Yamamoto Y. Determination of multielement concentrations in normal human organs from the Japanese. Biol Trace Elem Res. 2002 Winter;90(1-3):57-70. doi: 10.1385/BTER:90:1-3:57. PMID: 12666826.

68. Schroeder HA, Tipton IH, Nason AP. Trace metals in man: strontium and barium. J Chronic Dis. 1972 Sep;25(9):491-517. doi: 10.1016/0021-9681(72)90150-6. PMID: 4647214.

69. Zaichick V. Comparison of copper, iron, iodine, rubidium, strontium and zinc contents in thyroid tissue adjacent to thyroid malignant and benign nodules. British Journal of Healthcare

and Medical Research. 2022;9(1):88-97. doi: 10.14738/jbemi.91.11752.

70. Zaichick V. Comparison of calcium, chlorine, iodine, potassium, magnesium, manganese, and sodium in thyroid tissue adjacent to thyroid malignant and benign nodules. Biomedical Journal of Scientific & Technical Research 2022;42(1):33233-33239. doi: 10.26717/BJSTR.2022.42.006687.

71. Zaichick V. Application of neutron activation analysis for the comparison of eleven trace elements contents in thyroid tissue adjacent to thyroid malignant and benign nodules. International Journal of Radiology Sciences. 2022;4(1):6-12.

72. Zaichick V. Comparison of nineteen chemical elements in thyroid tissue adjacent to thyroid malignant and benign nodules using nuclear analytical methods. Journal of Medical and Biomedical Discoveries. 2022;5(1):121. doi: 10.29011/2688-8718.100021.

73. Zaichick V. Comparison of nineteen chemical elements in thyroid tissue adjacent to thyroid malignant and benign nodules using neutron activation analysis and inductively coupled plasma atomic emission spectrometry. International Journal of Multidisciplinary and Current Educational Research. 2022;4(1):219-229.

74. Zaichick V. Comparison of thirty trace elements contents in thyroid tissue adjacent to thyroid malignant and benign nodules. Archives of Clinical Case Studies and Case Reports. 2022;3(1):280-289.

75. Zaichick V. 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: 1997. p.123-133.

76. Zaichick V, Zaichick S. A search for losses of chemical elements during freeze-drying of biological materials. J Radioanal Nucl Chem. 1997;218(2):249-253. doi: 10.1007/BF02039345.

77. Zaichick V. Losses of chemical elements in biological samples under the dry aching process. Trace Elements in Medicine. 2004;5(3):17-22.

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