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Differences of Relationships between Iodine and Some Chemical Elements in Normal Thyroid and Thyroid Benign Nodules Revealed by Neutron Activation and Inductively Coupled Plasma Atomic Emission Spectrometry

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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 such chemical elements (ChEs) as Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V and Zn, as well as differences in I/ChEs content ratios in tissues of normal thyroid and TBN. Thyroid tissue levels of ChEs were prospectively evaluated in 105 apparently healthy persons and in 79 patients with TBN. Measurements were performed using neutron activation analysis combined with inductively coupled plasma atomic emission spectrometry. It was observed that in TBN the mass fraction of Al, B, Br, Cl, Cu, Fe, Li, Mn, Na, P, S, Si, V, and Zn were higher whereas mass fractions of Ca and I were lower than in normal tissues of the thyroid. It was found also that the I/Al, I/B, I/Br, I/Cl, I/Cu, I/K, I/Mg, I/Mn, I/Na, I/P, I/S, and I/Zn mass fraction ratios in TBN were significantly lower the normal levels. Furthermore, it was shown that the levels of Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V 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, such ChEs as Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V 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 ChE. An imbalance between I content and levels of other ChEs in the thyroid gland may be one of the causes of nodular neoplasms.

Keywords: Thyroid; Thyroid Benign Nodules; Chemical Elements; Energy-Dispersive Short-Term Neutron Activation Analysis; Inductively Coupled Plasma Atomic Emission Spectrometry

Abbreviations: TBN: Thyroid Benign Nodules; ChEs: Chemical Elements; INAA: Instrumental Neutron Activation Analysis; SLR: Short-Lived Radionuclides; ICP: Inductively Coupled Plasma; AES: Atomic Emission Spectrometry; CRM: Certified Reference Material; MPH: Mixed Polish Herbs; SD: Standard Deviation; SEM: Standard Error of The Mean; MRRC: Medical Radiological Research Centre.

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, 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 chemical elements (ChEs) 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 ChEs 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 ChEs can be essential or toxic (goitrogenic, mutagenic, carcinogenic) depending on specific tissue needs or tolerance, respectively [13]. Excessive accumulation or imbalance of ChEs 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 ChEs 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 ChEs of apparently healthy men and women was determined. As the results of these studies the age [25-35] and gender dependence of some ChEs was revealed [36-41]. In addition, it was found that the content of some ChEs of the thyroid gland with colloid goiter, thyroiditis and adenoma differs significantly from the levels of these ChEs in the normal thyroid gland [42-45].

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

It is generally accepted that the pathogenesis of TBN is multifactorial. The present study was conducted to elucidate the role of ChEs relationship disorders in the pathogenesis of TBN. With this in mind, our aim was to evaluate the content of aluminum (Al), boron (B), barium (Ba), bromine (Br), calcium (Ca), chlorine (Cl), coper (Cu), iron (Fe), iodine (I), potassium (K), lithium (Li), magnesium (Mg), manganese (Mn), sodium (Na), phosphorus (P), sulfur (S), silicon (Si), strontium (Sr), vanadium (V), and zinc (Zn) in TBN tissue using non-destructive instrumental neutron activation analysis with high resolution spectrometry of gamma-radiations from activated short-lived radionuclides (INAA-SLR) combined with inductively coupled plasma atomic emission spectrometry (ICP-AES) and calculate individual values of I/ChEs ratios. Another aim was to compare the levels of these I/ChEs ratios in TBN with those in the normal thyroid. Finally, differences in intrathyroidal relationships of ChEs contents, as well as in intrathyroidal relationships of I/ChEs content 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 MSD was 4812 years, range 30-64 years), thyroid adenoma (mean age MSD was 4111 years, range 22-55 years), and thyroiditis (mean age MSD was 399 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 ChEs content 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 4421 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 ChEs analysis. Samples intended for ChEs analysis were weighed, lyophilized, and homogenized [49]. The mass fraction of ChEs was calculated by the relative way of comparing between intensities of corresponding analytical signals in tissue samples and standards. Aliquots of commercial, chemically pure compounds and synthetic standard materials were used as standards [50].

Ten subsamples of the Certified Reference Material (CRM) IAEA H-4 (animal muscle), as well as Polish CRM INCT-SBF-4 Soya Bean Flour, INCT-TL-1 Tea Leaves, and INCT-MPH-2 Mixed Polish Herbs were analyzed to estimate the precision and accuracy of results. The CRM subsamples were prepared in the same way as the samples of dry homogenized thyroid tissue.

A horizontal channel equipped with the pneumatic rabbit system of the WWR-C research nuclear reactor was applied to determine the mass fraction of Br, Ca, I, K, Mg, Mn, and Na by INAA-SLR. The neutron flux in the channel was 1.7 × 1013n cm−2 s−1. Method ICP-AES were used to determine the Al, B, Ba, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fractions using the Spectrometer ICAP-61 (Thermo Jarrell Ash, USA). The determination of the ChE content in aqueous solutions was made by the quantitative method using calibration solutions (High Purity Standards, USA) of 0.5 and 10 mg/L of each element. The calculations of the tChE contents in the probe were carried out using software of a spectrometer (ThermoSPEC, version 4.1). Information detailing with the NAA-SLR and ICP-AES methods used, and other details of the analysis was presented in our previous studies on ChE contents in thyroid [18,27,28,46,47].

The tissue samples were prepared in duplicate and the average values of the ChEs 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 content of ChEs and I/ ChEs 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 ChEs contents and between different I/ ChEs content ratios in normal thyroid and TBN.

Results

Tables 1 and 2 represent 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 Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fraction (mg/kg, dry mass basis) and also I/Al, I/B, I/Ba, I/Br, I/Ca, I/Cl, I/Cu, I/Fe, I/K, I/Li, I/Mg, I/Mn, I/Na, I/P, I/S, I/Si, I/Sr, I/V, and I/ Zn mass fraction ratios in normal thyroid and TBN, respectively.

Element Ratio	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Al	10.5	13.4	1.8	0.8	69.3	6.35	1.19	52.9
B	0.476	0.434	0.058	0.2	2.3	0.3	0.2	1.73
Ba	1.12	1.15	0.15	0.048	5	0.68	0.0838	4.48
Br	14.9	11	1.2	1.9	54.1	11.6	2.56	49.3
Ca	1682	999	106	373	5582	1454	444	4183
Cl	3400	1452	174	1030	6000	3470	1244	5869
Cu	4.08	1.22	0.14	0.5	7.15	4.1	1.57	6.41
Fe	223	95	10	52	489	210	72.8	432
I	1841	1027	107	114	5061	1695	230	4232
K	6418	2625	290	1914	15293	5948	2947	13285
Li	0.0208	0.0155	0.0022	0.0015	0.0977	0.0178	0.0041	0.0487
Mg	296	134	16	66	930	284	95.8	541
Mn	1.28	0.56	0.07	0.47	4.04	1.15	0.537	2.23

Na	6928	1730	175	3686	13453	6835	3974	10709
P	4290	1578	207	496	8996	4221	1360	7323
S	8259	2002	263	644	11377	8399	3662	11208
Si	50.8	46.9	6.2	5.7	180	36	7.11	174
Sr	3.81	2.93	0.34	0.1	12.6	2.9	0.365	11.3
V	0.102	0.039	0.005	0.02	0.25	0.1	0.044	0.192
Zn	94.8	39.6	4.2	7.1	215	88.5	34.9	196
I/Al	421	494	71	5.14	2381	232	10.3	1565
I/B	5428	4430	633	193	17855	3800	415	16803
I/Ba	4509	9530	1375	147	60380	1718	190	26245
I/Br	174	126	14	5.86	576	144	7.61	478
I/Ca	1.46	1.32	0.15	0.136	7.45	1.08	0.164	5.29
I/Cl	0.714	0.54	0.065	0.0274	2.74	0.59	0.174	2.35
I/Cu	508	446	56	28.5	2756	418	46.6	1550
I/Fe	10.8	9.9	1.1	0.45	56.8	8.11	0.995	35.8
I/K	0.349	0.275	0.032	0.0209	1.51	0.276	0.027	0.897
I/Li	145191	175140	27692	7881	918667	100433	8231	638876
I/Mg	7.8	7.13	0.91	0.551	42.2	6.23	0.732	24.3
I/Mn	1635	1316	170	161	7066	1321	212	4976
I/Na	0.277	0.159	0.017	0.0162	0.728	0.246	0.0309	0.645
I/P	0.491	0.465	0.066	0.032	2.78	0.418	0.0523	1.29
I/S	0.251	0.303	0.043	0.023	2.14	0.194	0.0292	0.543
I/Si	83.9	103	15	1.31	368	34.3	2.98	351
I/Sr	1286	2818	355	37.4	20690	555	66.8	6387
I/V	20246	17571	2510	1222	77000	15836	1516	67243
I/Zn	23.4	17.6	2	2.03	109	22	2.95	65.2

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 1: Some statistical parameters of Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fraction (mg/kg, dry mass basis) and also I/Al, I/B, I/Ba, I/Br, I/Ca, I/Cl, I/Cu, I/Fe, I/K, I/Li, I/Mg, I/Mn, I/Na, I/P, I/S, I/Si, I/Sr, I/V, and I/ Zn mass fraction ratios in normal thyroid (n=105).

Element Ratio	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Al	27.3	23.6	4.2	6.6	95.1	19.5	7.07	82.2
B	1.97	1.69	0.31	0.81	7.3	1	0.875	5.63
Ba	1.7	2.42	0.43	0.18	11.7	0.96	0.265	0.988
Br	412	682	98	3.2	2628	64.5	8.35	2336
Ca	1313	860	131	52	4333	1169	120	3536
Cl	8231	3702	772	1757	16786	8326	2543	15157
Cu	10.2	9.2	1.7	2.9	35.2	6	3.04	34.9
Fe	332	332	39	52.3	1360	197	59.9	1285

I	1086	1219	139	29	8260	700	84.8	3734
K	7051	3955	577	797	23007	6298	1577	19908
Li	0.0295	0.0151	0.003	0.0073	0.068	0.0253	0.0096	0.0669
Mg	344	155	23	15	844	326	66.8	745
Mn	1.81	1.41	0.21	0.1	6.12	1.44	0.454	5.48
Na	10675	4434	647	2319	28481	10118	3690	18451
P	5145	1719	304	2890	9637	5030	2933	9091
S	10909	2177	385	5591	16706	10719	7353	15361
Si	90.4	68.3	12.3	7.8	346	83.7	13.4	223
Sr	5.35	7.09	0.99	0.42	32	2.52	0.788	29.3
V	0.152	0.066	0.012	0.043	0.37	0.15	0.0606	0.289
Zn	117.7	48.7	5.8	47	264	110	49.8	253
I/Al	105	185	33	4.49	1007	35.6	11.3	457
I/B	1184	1597	297	85.4	8260	574	99.8	5010
I/Ba	2590	4441	798	52.1	20094	653	92.7	16496
I/Br	29.3	66.3	9.6	0.18	374	5.82	0.281	243
I/Ca	1.5	2.12	0.33	0.0976	9.15	0.791	0.121	9.13
I/Cl	0.141	0.159	0.034	0.0161	0.623	0.0679	0.0191	0.511
I/Cu	252	315	60	9.7	1400	132	15.8	1036
I/Fe	7.62	13.3	1.6	0.181	96	3.23	0.245	28.7
I/K	0.218	0.26	0.039	0.00795	1.44	0.132	0.0131	0.79
I/Li	84846	204706	38013	4109	1131507	38857	5127	455169
I/Mg	4.52	5.51	0.82	0.173	28.9	2.8	0.226	18.4
I/Mn	1039	1282	198	33.1	5011	563	48.4	4368
I/Na	0.123	0.152	0.023	0.0134	0.918	0.0754	0.0166	0.413
I/P	0.313	0.306	0.055	0.0189	1.36	0.254	0.0285	1.14
I/S	0.137	0.154	0.028	0.00941	0.854	0.106	0.0237	0.461
I/Si	32.5	69.4	12.7	2.42	388	14.4	3.2	161
I/Sr	570	832	118	6.85	3591	202	12.3	2673
I/V	15709	36219	6970	558	192093	6578	1348	90743
I/Zn	11.4	13.1	1.6	0.337	63.1	7.11	1.12	54.7

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: Some statistical parameters of Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fraction (mg/kg, dry mass basis) and also I/Al, I/B, I/Ba, I/Br, I/Ca, I/Cl, I/Cu, I/Fe, I/K, I/Li, I/Mg, I/Mn, I/Na, I/P, I/S, I/Si, I/Sr, I/V, and I/ Zn mass fraction ratios in thyroid benign nodules (n=79).

The comparison of our results with published data for the Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn contents in the human thyroid and TBN is shown in Table 3.

Tissue	Published data [Reference]			This work
Element	Median of means (n)*	Minimum of means M or M±SD, (n)**	Maximum of means M or M±SD, (n)**	Males and females M±SD
NT				
Al	33.6 (12)	0.33 (-) [51]	420 (25) [52]	10.5±13.4
B	0.151 (2)	0.084 (3) [53]	0.46 (3) [53]	0.476±0.434
Ba	0.67 (7)	0.0084 (83) [54]	≤5.0 (16) [55]	1.12±1.15
Br	18.1 (11)	5.12 (44) [56]	284±44 (14) [57]	16.3±11.6
Ca	1600 (17)	840±240 (10) [58]	3800±320 (29) [58]	1663±999
Cl	6800 (5)	804±80 (4) [59]	8000 (-) [60]	3400±1452
Cu	6.1 (57)	1.42 (120) [61]	220±22 (10) [59]	3.93±1.43
Fe	252 (21)	56 (120) [61]	2444±700 (14) [57]	223±95
I	1888 (95)	159±8 (23) [62]	5772±2708 (50) [63]	1841±1027
K	4400 (17)	46.4±4.8 (4) [59]	6090 (17) [55]	6418±2625
Li	6.3 (2)	0.092 (-) [64]	12.6 (180) [65]	0.0208±0.0154
Mg	390 (16)	3.5 (-) [51]	840±400 (14) [66]	296±134
Mn	1.82 (36)	0.44±11 (12) [67]	69.2±7.2 (4) [59]	1.28±0.56
Na	8000 (9)	438 (-) [68]	10000±5000 (11) [66]	6928±1730
P	3200 (10)	16 (7) [69]	7520 (60) [56]	4290±1578
S	11000 (3)	4000 (-) [60]	11800 (44) [56]	8259±2002
Si	16.0 (3)	0.97 (-) [51]	143±6 (40) [70]	50.8±46.9
Sr	0.73 (9)	0.55±0.26 (21) [53]	46.8±4.8 (4) [59]	3.81±2.93
V	0.042 (6)	0.012 (2) [71]	18±2 (4) [59]	0.102±0.039
Zn	118 (51)	32 (120) [61]	820±204 (14) [57]	94.8±39.7
TBN				
Al	3.84 (5)	2.45 (123) [72]	840 (25) [52]	27.3±23.6
B	-	-	-	1.97±1.69
Ba	4.92 (1)	4.92±4.56 (51) [73]	4.92±4.56 (51) [73]	1.70±2.42
Br	528 (5)	20.2±11.3 (5) [74]	1277 (1) [75]	412±682
Ca	1664 (10)	1080 (2) [74]	8010±1290 (-) [76]	1313±860
Cl	864 (1)	864±84 (4) [59]	864±84 (4) [59]	8231±3702
Cu	9.84 (38)	0.84 (1) [65]	462 (101) [77]	10.2±9.2
Fe	296 (9)	54.6±36.1 (5) [74]	4848±3056 (11) [57]	332±332
I	812 (55)	77±14 (66) [78]	2800 (4) [79]	1086±1219
K	3100 (6)	72,8±7,2 (4) [59]	6030±620 (-) [76]	7051±3955
Li	-	-	-	0.0295±0.0151
Mg	834 (4)	588±388 (13) [80]	1616 (70) [81]	344±155

Mn	2.36 (21)	0.40±0.22 (64) [82]	57.6±6.0 (4) [59]	1.81±1.41
Na	3520 (1)	3520 (25) [52]	3520 (25) [52]	10675±4434
P	8200 (1)	8200±280 (-) [76]	8200±280 (-) [76]	5145±1719
S	10300 (1)	10300±340 (-) [76]	10300±340 (-) [76]	10909±2177
Si	64 (1)	45 (122) [83]	114 (122) [83]	90.4±68.3
Sr	1.64 (3)	1.32 (25) [52]	27.2±2.4 (4) [59]	5.35±7.09
V	10.4 (2)	3.92±8.84 (51) [73]	16.8±1.6 (4 [59]	0.152±0.066
Zn	104 (30)	22.4 (130) [82]	1236±560 (2) [84]	117.7±48.7

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

Table 3: Median, minimum and maximum value of means Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn contents in the normal thyroid (NT) and thyroid benign nodules (TBN) according to data from the literature in comparison with our results (mg/kg, dry mass basis).

Table 4 indicates the differences between mean values of Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fraction, as well as between mean values of I/Al, I/B, I/Ba, I/Br, I/Ca, I/Cl, I/Cu, I/Fe, I/K, I/Li, I/Mg, I/Mn, I/Na, I/P, I/S, I/Si, I/Sr, I/V, 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.

Element Ratio	**Thyroid tissue**				**Ratio**
	NT	**TBN**	**Student's t-test**	**U-test**	**TBN/NT**
	n=105	**n=79**	***p***	***p***	
Al	10.5±1.8	27.3±4.2	0.00059*	<0.01*	2.6
B	0.476±0.058	1.97±0.31	<0.00004*	<0.01*	4.14
Ba	1.12±0.15	1.70±0.43	0.21	>0.05	1.52
Br	14.9±1.2	412±98	0.00020*	<0.01*	27.7
Ca	1682±106	1313±131	0.031*	<0.05*	0.78
Cl	3400±174	8231±772	<0.00003*	<0.01*	2.42
Cu	4.08±0.14	10.2±1.7	0.0014*	<0.01*	2.5
Fe	223±10	332±39	0.0085*	<0.05*	1.49
I	1841±107	1086±139	<0.00003*	<0.01*	0.59
K	6418±290	7051±577	0.33	>0.05	1.1
Li	0.0208±0.0022	0.0295±0.0030	0.017*	<0.01*	1.42
Mg	296±16	344±23	0.091	>0.05	1.16
Mn	1.28±0.07	1.81±0.21	0.022*	<0.01*	1.41
Na	6928±175	10675±647	<0.00001*	<0.01*	1.54
P	4290±207	5145±304	0.023*	<0.01*	1.2
S	8259±263	10909±385	<0.00001*	<0.01*	1.32
Si	50.8±6.2	90.4±12.3	0.0060*	<0.05*	1.78
Sr	3.81±0.34	5.35±0.99	0.15	>0.05	1.4
V	0.102±0.005	0.152±0.012	0.00065*	<0.01*	1.49
Zn	94.8±4.2	117.7±5.8	0.0018*	<0.01*	1.24
I/Al	421±71	105±33	0.00014*	<0.01*	0.25
I/B	5428±633	1184±297	<0.00001*	<0.01*	0.22
I/Ba	4509±1375	2590±798	0.231	>0.05	0.57
I/Br	174±14	29.3±9.6	<0.00001*	<0.01*	0.17

I/Ca	1.46±0.15	1.50±0.33	0.903	>0.05	1.03
I/Cl	0.714±0.065	0.141±0.034	<0.00001*	<0.01*	0.2
I/Cu	508±56	252±60	0.0026*	<0.01*	0.5
I/Fe	10.8±1.1	7.62±1.6	0.114	>0.05	0.71
I/K	0.349±0.032	0.218±0.039	0.011*	<0.01*	0.62
I/Li	145191±27692	84846±38013	0.205	>0.05	0.58
I/Mg	7.80±0.91	4.52±0.82	0.0086*	<0.01*	0.58
I/Mn	1635±170	1039±198	0.025	<0.01*	0.64
I/Na	0.277±0.017	0.123±0.0230	<0.00001*	<0.01*	0.44
I/P	0.491±0.066	0.313±0.055	0.042*	<0.01*	0.64
I/S	0.251±0.043	0.137±0.028	0.029*	<0.01*	0.55
I/Si	83.9±15	32.5±12.7	0.010*	<0.01*	0.39
I/Sr	1286±355	570±118	0.059	>0.05	0.44
I/V	20246±2510	15709±6970	0.544	>0.05	0.78
I/Zn	23.4±2.0	11.4±1.6	<0.00001*	<0.01*	0.49

M – arithmetic mean, SEM – standard error of mean, * Significant values.
Table 4: Differences between mean values (M±SEM) of I/Al, I/B, I/Ba, I/Br, I/Ca, I/Cl, I/Cu, I/Fe, I/K, I/Li, I/Mg, I/Mn, I/Na, I/P, I/S, I/Si, I/Sr, I/V, and I/ Zn mass fraction ratios in normal thyroid (NT) and thyroid benign nodules (TBN).

Tables 5 and 6 depict the data of inter-thyroidal correlations (values of r – Pearson's coefficient of correlation) between all ChEs in normal thyroid and TBN, respectively.

El	Al	B	Ba	Br	Ca	Cl	Cu	Fe	I	K
Al	1	0.03	0.17	0.1	-0.02	0.01	0.26[a]	0.50[c]	-0.33[b]	0.31[a]
B	0,03	1	0.59[c]	0.1	0.02	-0.45[c]	-0.19	-0.04	0.15	0.11
Ba	0,17	0,59	1	0.07	0.1	-0.21	0.03	0.01	0.2	0.23
Br	0,10	0,10	0,07	1	0.11	-0.08	0.26[a]	0.04	0.04	0.09
Ca	-0,02	0,02	0,10	0,11	1	-0.35b	-0.26[a]	-0.1	0.2	-0.11
Cl	0,01	-0,45	-0,21	-0,08	-0,35	1	0.17	0.15	0.11	-0.40[b]
Cu	0,26	-0,19	0,03	0,26	-0,26	0,17	1	0.3	-0.17	0.19
Fe	0,50	-0,04	0,01	0,04	-0,10	0,15	0,30	1	-0.26[a]	0.16
I	-0,33	0,15	0,20	0,04	0,20	0,11	-0,17	-0,26	1	-0.17
K	0,31	0.11	0.23	0.09	-0.11	-0.4	0.19	0.16	-0.17	1
Li	0.63[c]	0.21	0.29[a]	-0.09	0.12	-0.19	0.17	0.19	-0.14	0.38[b]
Mg	0.27[a]	0.03	0.06	-0.24	0.26[a]	0.16	0.26[a]	0.27[a]	-0.12	0.41
Mn	0.27[a]	0.14	0.08	0.30[a]	0.08	-0.07	0.19	0.35[b]	-0.17	0.02
Na	0.40[b]	0.05	-0.21	-0.02	-0.16	0.47[c]	0.29[a]	0.24	0.09	-0.03
P	0.32[b]	0.07	0.18	0.14	-0.19	0.04	0.55[c]	0.34[b]	-0.16	0.70[c]
S	-0.11	0.19	-0.05	-0.19	0.15	-0.07	0.01	-0.07	0.28[a]	0.34[b]
Si	0.30[a]	0.40[b]	0.58[c]	0.12	-0.1	0.01	0.15	0.42[c]	-0.1	0.14
Sr	0.09	-0.03	-0.14	0.24	0.31[a]	-0.32[b]	0.05	-0.03	-0.09	0.14
V	0.35[b]	-0.03	0.07	-0.12	-0.03	0.28[a]	0.27[a]	0.42[c]	-0.15	0.19
Zn	0.24	-0.1	0.13	0.05	0.12	-0.15	0.45[c]	0.16	0.01	0.15
El	Li	Mg	Mn	Na	P	S	Si	Sr	V	Zn
Al	0,63	0,27	0,27	0,40	0,32	-0,11	0,30	0,09	0,35	0,24
B	0,21	0,03	0,14	0,05	0,07	0,19	0,40	-0,03	-0,03	-0,10

Ba	0,29	0,06	0,08	-0,21	0,18	-0,05	0,58	-0,14	0,07	0,13
Br	-0,09	-0,24	0,30	-0,02	0,14	-0,19	0,12	0,24	-0,12	0,05
Ca	0,12	0,26	0,08	-0,16	-0,19	0,15	-0,10	0,31	-0,03	0,12
Cl	-0,19	0,16	-0,07	0,47	0,04	-0,07	0,01	-0,32	0,28	-0,15
Cu	0,17	0,26	0,19	0,29	0,55	0,01	0,15	0,05	0,27	0,45
Fe	0,19	0,27	0,35	0,24	0,34	-0,07	0,42	-0,03	0,42	0,16
I	-0,14	-0,12	-0,17	0,09	-0,16	0,28	-0,10	-0,09	-0,15	0,01
K	0,38	0,41	0,02	-0,03	0,70	0,34	0,14	0,14	0,19	0,15
Li	1	0.43[c]	0.23	0.25[a]	0.29[a]	0.21	0.13	0.14	0.33[b]	0.36[b]
Mg	0,43	1	0.12	0.23	0.61[c]	0.28[a]	0.14	0.22	0.13	0.35[b]
Mn	0,23	0,12	1	0.02	0.41[c]	-0.09	0.31[a]	0.16	0.22	0.04
Na	0,25	0,23	0,02	1	0.47[c]	0.28[a]	-0.03	-0.13	0.29[a]	0.18
P	0,29	0,61	0,41	0,47	1	0.19	0.28[a]	0.04	0.29[a]	0.43[c]
S	0,21	0,28	-0,09	0,28	0,19	1	-0.29[a]	0.19	0.16	0.21
Si	0,13	0,14	0,31	-0,03	0,28	0,29	1	-0.16	0.35[b]	-0.1
Sr	0,14	0,22	0,16	-0,13	0,04	0,19	-0,16	1	0.05	0.17
V	0,33	0,13	0,22	0,29	0,29	0,16	0,35	0,05	1	-0.01
Zn	0,36	0,35	0,04	0,18	0,43	0,21	-0,1	0,17	-0,01	1

El – element, Significant values: a $p<0.05$, b $p<0.01$, c $p<0.001$.

Table 5: Intercorrelations of the chemical element mass fractions in the normal thyroid (r – coefficient of correlation).

El	Al	B	Ba	Br	Ca	Cl	Cu	Fe	I	K
Al	1	0.38[b]	0.60[c]	-0.22	-0.07	0.2	0.01	0.29[a]	-0.08	0.2
B	0.38[b]	1	0.35[b]	-0.2	-0.04	-0.18	0.08	-0.06	0.11	-0.01
Ba	0.60[c]	0.35[b]	1	0.09	-0.02	-0.40[b]	-0.04	-0.05	-0.12	-0.06
Br	-0.22	-0.2	0.09	1	-0.05	0.09	0.08	-0.12	0.04	0.36[b]
Ca	-0.07	-0.04	-0.02	-0.05	1	0.32[a]	-0.18	-0.16	0.41[b]	-0.27[a]
Cl	0.2	-0.18	-0.40[b]	0.09	0.32[a]	1	0.31[a]	0.55[c]	-0.03	0.21
Cu	0.01	0.08	-0.04	0.08	-0.18	0.31[a]	1	0.16	-0.06	0.22
Fe	0.29[a]	-0.06	-0.05	-0.12	-0.16	0.55[c]	0.16	1	-0.13	-0.03
I	-0.08	-0.01	-0.12	0.04	0.41[b]	-0.03	-0.06	-0.13	1	-0.08
K	0.2	-0,01	-0.06	0.36[b]	-0.27[a]	0.21	0.22	-0.03	-0.08	1
Li	0.41[b]	0.17	0.52[c]	-0.09	-0.37[b]	-0,41[b]	0.2	0.37[b]	-0.13	0.32[a]
Mg	0.04	-0.24	-0.13	0.22	-0.2	0.1	-0.21	-0.07	0.04	0.74[c]
Mn	0.21	0.33[a]	0.31[a]	0.08	0.25	0.16	0.38[b]	-0.19	0.09	0.53[c]
Na	0.06	0.03	-0.09	0.29[a]	0.16	0.81[c]	0.60[c]	0.05	0.12	0.13
P	0.08	0.13	-0.05	0.01	-0.09	0.04	0.28[a]	-0.09	0.08	0.82[c]
S	0.02	0.19	0.1	-0.06	0.01	-0.40[b]	0.03	-0.38[b]	0.13	0.2
Si	0.64[c]	0.21	0.65[c]	0.05	-0.06	-0.04	0.17	0.24	-0.06	0.19
Sr	0.14	0.02	0.07	-0.06	0.06	0.06	0.37[b]	0.13	0.02	-0.01
V	0.11	0.15	0.60[c]	0.26	-0.1	0.11	0.07	0.03	-0.36[b]	0.08
Zn	0.01	0.03	-0.02	0.30[a]	0.2	0.09	0.04	-0.23	0.09	-0.18
El	Li	Mg	Mn	Na	P	S	Si	Sr	V	Zn
Al	0.41[b]	0.04	0.21	0.06	0.08	0.02	0.64[c]	0.14	0.11	0.01
B	0.17	-0.24	0.33[a]	0.03	0.13	0.19	0.21	0.02	0.15	0.03

Ba	0.52[c]	-0.13	0.31[a]	-0.09	-0.05	0.1	0.65[c]	0.07	0.60[c]	-0.02
Br	-0.09	0.22	0.08	0.29[a]	0.01	-0.06	0.05	-0.06	0.26	0.30[a]
Ca	-0.37[b]	-0.2	0.25	0.16	-0.09	0.01	-0.06	0.06	-0.1	0.2
Cl	-0,41[b]	0.1	0.16	0.81[c]	0.04	-0.40[b]	-0.04	0.06	0.11	0.09
Cu	0.2	-0.21	0.38[b]	0.60[c]	0.28[a]	0.03	0.17	0.37[b]	0.07	0.04
Fe	0.37[b]	-0.07	-0.19	0.05	-0.09	-0.38[b]	0.24	0.13	0.03	-0.23
I	-0.13	0.04	0.09	0.12	0.08	0.13	-0.06	0.02	-0.36[b]	0.09
K	0.32[a]	0.74[c]	0.53[c]	0.13	0.82[c]	0.2	0.19	-0.01	0.08	-0.18
Li	1	-0.15	0.35[b]	0.04	0.03	0.06	0.44[b]	0.23	-0.07	-0.28[a]
Mg	-0.15	1	0.35[b]	-0.03	0.47[c]	-0.01	0.11	0.06	0.11	-0.22
Mn	0.35[b]	0.35[b]	1	0.31[a]	0.56[c]	0.39[b]	0.18	0.1	0.32[a]	0.09
Na	0.04	-0.03	0.31[a]	1	0.01	0.27[a]	-0.1	0.55[c]	0.06	0.16
P	0.03	0.47[c]	0.56[c]	0.01	1	0.26	0.01	-0.11	0.1	-0.01
S	0.06	-0.01	0.39[b]	0.27[a]	0.26	1	-0.07	0.01	0.22	0.19
Si	0.44[b]	0.11	0.18	-0.1	0.01	-0.07	1	-0.08	0.14	-0.18
Sr	0.23	0.06	0.1	0.55[c]	-0.11	0.01	-0.08	1	0.06	-0.11
V	-0.07	0.11	0.32[a]	0.06	0.1	0.22	0.14	0.06	1	-0.01
Zn	-0.28[a]	-0.22	0.09	0.16	-0.01	0.19	-0.18	-0.11	-0.01	1

El – element, Significant values: a $p<0.05$, b $p<0.01$, c $p<0.001$.

Table 6: Intercorrelations of the chemical element mass fractions in thyroid benign nodules (r – coefficient of correlation).

The data of inter-thyroidal correlations (values of r – Pearson's coefficient of correlation) between all I/ChEs mass fraction ratios identified by us in normal thyroid and TBN are presented in Tables 7 and 8, respectively.

Ratio	I/Al	I/B	I/Ba	I/Br	I/Ca	I/Cl	I/Cu	I/Fe	I/K
I/Al	**1**	0.62[c]	0.16	0.50[c]	0.45[c]	0.48[c]	0.36[b]	0.58[c]	0.53[c]
I/B	0.62[c]	**1**	0.26	0.50[c]	0.36[b]	0.30[a]	0.41[b]	0.58[c]	0.64[c]
I/Ba	0.16	0.26	**1**	0.09	0.24	0.04	0.57[c]	0.17	0.33[a]
I/Br	0.50[c]	0.50[c]	0.09	**1**	0.28[a]	0.29[a]	0.29[a]	0.40[b]	0.35[b]
I/Ca	0.45[c]	0.36[b]	0.24	0.28[a]	**1**	0.08	0.42[b]	0.47[c]	0.55[c]
I/Cl	0.48[c]	0.30[a]	0.04	0.29[a]	0.08	**1**	0.33[a]	0.37[b]	0.29[a]
I/Cu	0.36[b]	0.41[b]	0.57[c]	0.29[a]	0.42[b]	0.33[a]	**1**	0.42[b]	0.64[c]
I/Fe	0.58[c]	0.58[c]	0.17	0.40[b]	0.47[c]	0.37[b]	0.42[b]	**1**	0.75[c]
I/K	0.53[c]	0.64[c]	0.33[a]	0.35[b]	0.55[c]	0.29[a]	0.64[c]	0.75[c]	**1**
I/Li	0.44[b]	0.45[b]	0.51[c]	0.23	0.47[c]	0.07	0.84[c]	0.18	0.51[c]
I/Mg	0.64[c]	0.59[c]	0.41[b]	0.15	0.54[c]	0.48[c]	0.61[c]	0.58[c]	0.77[c]
I/Mn	0.50[c]	0.56[c]	0.55[c]	0.39[b]	0.72[c]	0.49[c]	0.52[c]	0.68[c]	0.67[c]
I/Na	0.54[c]	0.56[c]	0.23	0.47[c]	0.48[c]	0.77[c]	0.66[c]	0.65[c]	0.73[c]
I/P	0.42[b]	0.45[c]	0.55[c]	0.26	0.43[b]	0.30[a]	0.94[c]	0.42[b]	0.70[c]
I/S	0.26	0.26	0.42[b]	0.15	0.37[b]	0.11	0.91[c]	0.24	0.45[c]
I/Si	0.70[c]	0.70[c]	0.61[c]	0.47[c]	0.34[a]	0.43[b]	0.53[c]	0.49[c]	0.60[c]
I/Sr	0.37[b]	0.34[a]	0.37[b]	0.07	0.16	0.34[a]	0.33[a]	0.14	0.11
I/V	0.52[c]	0.47[c]	0.34[a]	0.39[b]	0.46[c]	0.58[c]	0.78[c]	0.58[c]	0.77[c]

I/Zn	0.40[b]	0.48[c]	0.36[b]	0.29	0.60[c]	0.32[a]	0.62[c]	0.49[c]	0.66[c]
Ratio	**I/Li**	**I/Mg**	**{/Mn**	**I/Na**	**I/P**	**I/S**	**I/Si**	**I/Sr**	**I/V**
I/Al	0.44[b]	0.64[c]	0.50[c]	0.54[c]	0.42[b]	0.26	0.70[c]	0.37[b]	0.52[c]
I/B	0.45[b]	0.59[c]	0.56[c]	0.56[c]	0.45[c]	0.26	0.70[c]	0.34[a]	0.47[c]
I/Ba	0.51[c]	0.41[b]	0.55[c]	0.23	0.55[c]	0.42[b]	0.61[c]	0.37[b]	0.34[a]
I/Br	0.23	0.15	0.39[b]	0.47[c]	0.26	0.15	0.47[c]	0.07	0.39[b]
I/Ca	0.47[c]	0.54[c]	0.72[c]	0.48[c]	0.43[b]	0.37[b]	0.34[a]	0.16	0.46[c]
I/Cl	0.07	0.48[c]	0.49[c]	0.77[c]	0.30[a]	0.11	0.43[b]	0.34[a]	0.58[c]
I/Cu	0.84[c]	0.61[c]	0.52[c]	0.66[c]	0.94[c]	0.91[c]	0.53[c]	0.33[a]	0.78[c]
I/Fe	0.18	0.58[c]	0.68[c]	0.65[c]	0.42[b]	0.24	0.49[c]	0.14	0.58[c]
I/K	0.51[c]	0.77[c]	0.67[c]	0.73[c]	0.70[c]	0.45[c]	0.60[c]	0.11	0.77[c]
I/Li	**1**	0.62[c]	0.40[b]	0.47[b]	0.90[c]	0.83[c]	0.53[c]	0.78[c]	0.55[c]
I/Mg	0.62[c]	**1**	0.60[c]	0.63[c]	0.67[c]	0.41[b]	0.66[c]	0.51[c]	0.65[c]
I/Mn	0.40[b]	0.60[c]	**1**	0.69[c]	0.52[c]	0.25	0.64[c]	0.36[b]	0.54[c]
I/Na	0.47[b]	0.63[c]	0.69[c]	**1**	0.67[c]	0.48[c]	0.51[c]	0.34[a]	0.82[c]
I/P	0.90[c]	0.67[c]	0.52[c]	0.67[c]	**1**	0.90[c]	0.53[c]	0.78[c]	0.77[c]
I/S	0.83[c]	0.41[b]	0.25	0.48[c]	0.90[c]	**1**	0.34[a]	0.86[c]	0.70[c]
I/Si	0.53[c]	0.66[c]	0.64[c]	0.51[c]	0.53[c]	0.34[a]	**1**	0.39[b]	0.48[c]
I/Sr	0.78[c]	0.51[c]	0.36[b]	0.34[a]	0.78[c]	0.86[c]	0.39[b]	**1**	0.66[c]
I/V	0.55[c]	0.65[c]	0.54[c]	0.82[c]	0.77[c]	0.70[c]	0.48[c]	0.66[c]	**1**
I/Zn	0.62[c]	0.77[c]	0.57[c]	0.65[c]	0.61[c]	0.46[c]	0.49[c]	0.27[a]	0.62[c]

Significant values: a <0.05, b <0.01, c <0.001.

Table 7: Intercorrelations of the iodine/chemical element mass fraction ratios in the normal thyroid (r – coefficient of correlation).

Ratio	I/Al	I/B	I/Ba	I/Br	I/Ca	I/Cl	I/Cu	I/Fe	I/K
I/Al	**1**	0.94[c]	0.68[c]	0.12	0.41[a]	0.47[b]	0.85[c]	0.96[c]	0.89[c]
I/B	0.94[c]	**1**	0.76[c]	-0.14	0.47[b]	0.41[a]	0.85[c]	0.90[c]	0.85[c]
I/Ba	0.68[c]	0.76[c]	**1**	0.80[c]	0.71[c]	0.41[b]	0.86[c]	0.69[c]	0.74[c]
I/Br	0.12	-0.14	0.80[c]	**1**	0.15	0.76[c]	0.72[c]	0.43[b]	0.70[c]
I/Ca	0.41[a]	0.47[b]	0.71[c]	0.15	**1**	0.79[c]	0.62[b]	0.24	0.41[a]
I/Cl	0.47[b]	0.41[a]	0.41[b]	0.76[c]	0.79[c]	**1**	0.28	0.70[c]	0.83[c]
I/Cu	0.85[c]	0.85[c]	0.86[c]	0.72[c]	0.62[b]	0.28	**1**	0.82[c]	0.92[c]
I/Fe	0.96[c]	0.90[c]	0.69[c]	0.43[b]	0.24	0.70[c]	0.82[c]	**1**	0.85[c]
I/K	0.89[c]	0.85[c]	0.74[c]	0.70[c]	0.41[a]	0.83[c]	0.92[c]	0.85[c]	**1**
I/Li	0.94[c]	0.89[c]	0.60[c]	0.79[c]	0.33	0.63[c]	0.80[c]	0.93[c]	0.90[c]
I/Mg	0.74[c]	0.73[c]	0.77[c]	0.49[b]	0.24	0.34	0.81[c]	0.79[c]	0.54[b]
I/Mn	0.52[b]	0.43[b]	0.68[c]	0.48[b]	0.58[c]	0.54[b]	0.86[c]	0.3	0.66[c]
I/Na	0.90[c]	0.87[c]	0.70[c]	0.69[c]	0.42[a]	0.98[c]	0.90[c]	0.87[c]	0.94[c]
I/P	0.80[c]	0.82[c]	0.87[c]	0.71[c]	0.73[c]	0.75[c]	0.95[c]	0.78[c]	0.93[c]
I/S	0.90[c]	0.90[c]	0.75[c]	0.70[c]	0.59[c]	0.83[c]	0.90[c]	0.91[c]	0.98[c]
I/Si	0.94[c]	0.88[c]	0.62[c]	0.38[c]	0.31	0.57[b]	0.77[c]	0.94[c]	0.86[c]
I/Sr	0.68[c]	0.71[c]	0.71[c]	0.06	0.43[a]	0.78[c]	0.73[c]	0.72[c]	0.68[c]
I/V	0.96[c]	0.92[c]	0.68[c]	0.61[c]	0.44[a]	0.69[c]	0.84[c]	0.97[c]	0.91[c]

I/Zn	0.69[c]	0.71[c]	0.83[c]	0.80[c]	0.45[a]	0.88[c]	0.89[c]	0.70[c]	0.90[c]
Ratio	**I/Li**	**I/Mg**	**{/Mn**	**I/Na**	**I/P**	**I/S**	**I/Si**	**I/Sr**	**I/V**
I/Al	0.94[c]	0.74[c]	0.52[b]	0.90[c]	0.80[c]	0.90[c]	0.94[c]	0.68[c]	0.96[c]
I/B	0.89[c]	0.73[c]	0.43[b]	0.87[c]	0.82[c]	0.90[c]	0.88[c]	0.71[c]	0.92[c]
I/Ba	0.60[c]	0.77[c]	0.68[c]	0.70[c]	0.87[c]	0.75[c]	0.62[c]	0.71[c]	0.68[c]
I/Br	0.79[c]	0.49[b]	0.48[b]	0.69[c]	0.71[c]	0.70[c]	0.38[c]	0.06	0.61[c]
I/Ca	0.33	0.24	0.58[c]	0.42[a]	0.73[c]	0.59[c]	0.31	0.43[a]	0.44[a]
I/Cl	0.63[c]	0.34	0.54[b]	0.98[c]	0.75[c]	0.83[c]	0.57[b]	0.78[c]	0.69[c]
I/Cu	0.80[c]	0.81[c]	0.86[c]	0.90[c]	0.95[c]	0.90[c]	0.77[c]	0.73[c]	0.84[c]
I/Fe	0.93[c]	0.79[c]	0.3	0.87[c]	0.78[c]	0.91[c]	0.94[c]	0.72[c]	0.97[c]
I/K	0.90[c]	0.54[b]	0.66[c]	0.94[c]	0.93[c]	0.98[c]	0.86[c]	0.68[c]	0.91[c]
I/Li	**1**	0.68[c]	0.77[c]	0.93[c]	0.73[c]	0.93[c]	0.98[c]	0.64[c]	0.99[c]
I/Mg	0.68[c]	**1**	0.32[a]	0.55[c]	0.89[c]	0.87[c]	0.69[c]	0.77[c]	0.82[c]
I/Mn	0.77[c]	0.32[a]	**1**	0.71[c]	0.85[c]	0.77[c]	0.3	0.34[a]	0.84[c]
I/Na	0.93[c]	0.55[c]	0.71[c]	**1**	0.88[c]	0.98[c]	0.89[c]	0.68[c]	0.94[c]
I/P	0.73[c]	0.89[c]	0.85[c]	0.88[c]	**1**	0.90[c]	0.71[c]	0.72[c]	0.79[c]
I/S	0.93[c]	0.87[c]	0.77[c]	0.98[c]	0.90[c]	**1**	0.90[c]	0.70[c]	0.95[c]
I/Si	0.98[c]	0.69[c]	0.3	0.89[c]	0.71[c]	0.90[c]	**1**	0,59[c]	0.97[c]
I/Sr	0.64[c]	0.77[c]	0.34[a]	0.68[c]	0.72[c]	0.70[c]	0,59[c]	**1**	0.72[c]
I/V	0.99[c]	0.82[c]	0.84[c]	0.94[c]	0.79[c]	0.95[c]	0.97[c]	0.72[c]	**1**
I/Zn	0.71[c]	0.86[c]	0.66[c]	0.89[c]	0.92[c]	0.89[c]	0.67[c]	0.57[c]	0.77[c]

Significant values: a <0.05, b <0.01, c <0.001.

Table 8: Intercorrelations of the iodine/chemical element mass fraction ratios in thyroid benign nodules (r – coefficient of correlation).

Discussion

Precision and Accuracy of Results

Previously found good agreement of our results for the Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fractions with the certified values of CRM IAEA H-4 Animal Muscle, INCT-SBF-4 Soya Bean Flour, INCT-TL-1 Tea Leaves, and INCT-MPH-2 Mixed Polish Herbs [18,27,28,46,47] demonstrates an acceptable precision and accuracy of the results obtained in the study and presented in Tables 1-8.

The content of ChEs 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 Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn, as well as I/Al, I/B, I/Ba, I/Br, I/Ca, I/Cl, I/Cu, I/Fe, I/K, I/Li, I/Mg, I/Mn, I/Na, I/P, I/S, I/Si, I/Sr, I/V, and I/ Zn mass fraction ratios in normal thyroid (Table 1) 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 ChEs 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 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 ChEs content and I/ChE content ratio in normal and pathological thyroid tissue.

Comparison with Published Data

The obtained means for Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fraction, as shown in Table 3, agreed well with the medians of mean values reported by other researches for the human thyroid, including samples received from persons who died from different non-thyroid diseases [51-71]. The obtained mean for Li was two orders of magnitude lower the median of previously reported data. Moreover, it was outside the range of previously reported means.

In TBN tissues (Table 3) our results were comparable with published data for Al, Ba, Br, Ca, Cu, I, Mn, S, Sr, and Zn contents [52,57,59,65,72-84]. Our mean of K content was outside the range of published means [59,76], but close to the upper limit of this range, while the mean of Mg content was slightly below the minimum value of the reported range of means [80,81]. This work mean of P content was slightly below the only reported result [76]. The obtained means for Cl and Na were 9.5 and 3.0 times higher, respectively, than the only reported result [59] and [52], respectively, while obtained means for V was almost two orders of magnitude lower the median of previously reported data. No published data referring B and Li contents in TBN were found. Some values for means of ChEs mass fractions reported were not expressed on a dry mass basis. Because of this we recalculated these values using published data for water (75%) [85] and ash (4.16% on dry mass basis) [86] contents in thyroid of adults.

No published data referring to I/Al, I/B, I/Ba, I/Br, I/Ca, I/Cl, I/Cu, I/Fe, I/K, I/Li, I/Mg, I/Mn, I/Na, I/P, I/S, I/Si, I/Sr, I/V, and I/Zn mass fraction ratios 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 content of ChEs 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 [87-92]. The range of means of Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn, reported in the literature for normal thyroid and TBN, vary widely (Table 3). This can be explained by the dependence of the ChEs 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 ChEs are lost as a result of such processing. This applies not only to such volatile halogens as Br and I, but also to other ChEs studied in the present work [93-95].

Differences between the Normal Thyroid and TBN in the Contents of TEs and I/TEs Content Ratios

From Table 4, it is observed that in TBN the mass fraction of Al, B, Br, Cl, Cu, Fe, Li, Mn, Na, P, S, Si, V, and Zn were 2.6, 4.1, 27.7, 2.4, 2.5, 1.5, 1.4, 1.4, 1.5, 1.2, 1.3, 1.8, 1.5, and 1.2 times, respectively, higher whereas mass fractions of Ca and I were 22% and 41% , respectively, lower than in normal tissues of the thyroid. Since the changes in the content Al, B, Br, Cl, Cu, Mn, Na, P, S, Si, and Zn, on the one hand, and I, on the other hand, in TBN were in different directions, the I/Al, I/B, I/Br, I/Cl, I/Cu, I/Mn, I/Na, I/P, I/S, and I/Zn ratios in TBN also differed significantly from the norm (Table 4). Moreover, the I/K and I/Mg mass fraction ratios in TBN was 38% and 42%, respectively, below the normal level. This confirmed that the I/ChEs ratios can be more sensitive parameters than the absolute values of the ChEs content in thyroid tissue.

Generally, elevated or decreased levels of ChEs 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 ChEs in the occurrence of TBN by the low or high level of ChEs in TBN tissues. In our opinion, the abnormal levels of many ChEs 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 level of ChEs in pathologically altered tissue is the cause or consequence of the disease.

Relationships between Trace Elements in Normal Thyroid and TBN

Among the twenty ChEs studied in the normal thyroid gland, a direct correlation was found only between I and S and an inverse correlation between I and Al and between I and Fe (Table 5). In TBN, these correlations were not found, but there was a direct correlation between I and Ca and an inverse correlation between I and V (Table 6). Also, many of the other ChE correlations found in normal thyroid tissue (Table 5) were not found in TBN, but other correlations emerged (Table 6).

The absence of correlations between I and many ChEs in the normal thyroid gland suggested that the content of B, Ba, Br, Ca, Cl, Cu, K, Mg, Mn, Na, P, S, Si, Sr, V, and Zn in the thyroid gland does not depend on the content of iodine. However, this is not quite true. When the content of the investigated ChEs was reduced to the content of I (I/ChE ratio), it turned out that there were a large number of direct and reverse correlation between the normalized values of the ChEs content (Table 7). As regards the I/ChEs ratios in TBN, compared to the normal thyroid, some correlations disappeared, while others emerged (Table 8). It followed that the levels of Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Mg, Mn, Na, P, S, Si, Sr, V, and Zn in the normal thyroid gland and TBN are interrelated and depend on the content of I.

Conclusion

In this work, ChEs analyses were carried out in the tissue samples of normal thyroid and TBN using the combination of nondestructive and destructive methods. It was shown that the combination of INAA-SLR (non-destructive method) and ICP-AES (method requires acid dissolution of the sample) is a useful analytical tool for determining the content of ChEs in thyroid tissue samples, including core biopsy. This method allows determine content of Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V and Zn (twenty ChEs),

Our data reveal that in TBN the mass fraction of Al, B, Br, Cl, Cu, Fe, Li, Mn, Na, P, S, Si, V, and Zn were higher whereas mass fractions of Ca and I were lower than in normal tissues of the thyroid. It was found also that the I/Al, I/B, I/Br, I/Cl, I/Cu, I/K, I/Mg, I/Mn, I/Na, I/P, I/S, and I/Zn mass fraction ratios in TBN were significantly lower the normal levels. These changes can potentially be used as TBN markers. Furthermore, it was shown that the levels of Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V 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, such ChEs as Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V 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 ChEs.

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Conflict of Interest

The author has not declared any conflict of interests.

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