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Vladimir Zaichick*
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Differences of Relationships Between Iodine and Some Chemical Elements in Normal Thyroid and Thyroid Benign Nodules Revealed by X-Ray Fluorescence and Neutron Activation Analysis

Vladimir Zaichick

Radionuclide Diagnostics Department, Medical Radiological Research Centre, Russia.

***Corresponding Author:** Vladimir Zaichick, Radionuclide Diagnostics Department, Medical Radiological Research Centre, Russia.

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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 Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, 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 X-ray fluorescence combined with neutron activation analysis. that in TBN the mass fraction of Ag, Br, Cl, Co, Cr, Cu, Fe, Hg, Mn, Na, and Sc 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/Ag, I/Br, I/Cl, I/Co, I/Cu, I/Fe, I/Hg, I/K, I/Na, I/Rb, I/Se, and I/Zn mass fraction ratios in TBN were significantly lower the normal levels. Furthermore, it was shown that the levels of Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, 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, such ChEs as Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, 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. An imbalance between I content and levels of other ChEs in the thyroid gland may be one of the causes of nodular neoplasms.

Key words: thyroid; thyroid benign nodules; chemical elements; neutron activation analysis; X-ray fluorescence analysis

1- 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 silver (Ag), calcium (Ca), chlorine (Cl), cobalt (Co), chromium (Cr), cooper (Cu), iron (Fe), mercury (Hg), iodine (I), potassium (K), magnesium (Mg), manganese (Mn), sodium (Na), rubidium (Rb), ammonium (Sb), scandium (Sc), selenium (Se), strontium (Sr), and zinc (Zn) contents in TBN tissue using a non-destructive energy-dispersive X-Ray fluorescent analysis (EDXRF) combined with instrumental neutron activation analysis with high resolution spectrometry of short- and long-lived radionuclides (INAA-SLR and INAA-LLR, respectively). 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.

2. 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 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 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 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 sub-samples of certified reference material (CRM) of the International Atomic Energy Agency (IAEA) IAEA H-4 (animal muscle) and IAEA HH-1 (human hair) 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 Cu, Fe, Rb, Sr, and Zn were determined by EDXRF. Details of the relevant facility for this method, source with ^{109}Cd radionuclide, methods of analysis and the results of quality control were presented in our earlier publications concerning the EDXRF of ChE contents in human thyroid [25,26].
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 neutron flux, nuclear reactions, radionuclides, gamma-energies, spectrometric unit, sample preparation and measurement were presented in our earlier publications concerning the INAA-SLR of ChE contents in human thyroid [27,28].
In a few days after non-destructive INAA-SLR all thyroid samples were repacked and used for INAA-LLR. A vertical channel of the WWR-c research nuclear reactor (Branch of Karpov Institute, Obninsk).was applied to determine the content of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn by INAA-LLR. Details of used neutron flux, nuclear reactions, radionuclides, gamma-energies, spectrometric unit, sample preparation and measurement were presented in our earlier publications concerning the INAA-LLR of ChE contents in human thyroid [29,30].
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.

3. 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 Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn mass fraction (mg/kg, dry mass basis) and also I/Ag, I/Br, I/Ca, I/Cl, I/ Co, I/Cr, I/Cu, I/Fe, I/Hg, I/K, I/Mg, I/Mn, I/Na, I/Rb, I/Sb, I/Sc, I/Se, I/Sr, and I/Zn mass fraction ratios in normal thyroid and TBN, respectively.

Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Ag	0.0151	0.0140	0.0016	0.0012	0.0800	0.0121	0.0017	0.0454
Br	14.9	11.0	1.2	1.90	54.1	11.6	2.56	49.3
Ca	1711	1022	109	414	6230	1458	460	3805
Cl	3400	1452	174	1030	6000	3470	1244	5869
Co	0.0399	0.0271	0.0030	0.0046	0.140	0.0327	0.0134	0.124
Cr	0.539	0.272	0.032	0.130	1.30	0.477	0.158	1.08
Cu	4.23	1.52	0.18	0.500	7.50	4.15	1.57	7.27
Fe	223	93	10	51.0	512	221	74.2	433
Hg	0.0421	0.0358	0.0041	0.0065	0.180	0.0304	0.0091	0.150
I	1841	1027	107	114	5061	1695	230	4232
K	6071	2773	306	1740	14300	5477	2541	13285
Mg	285	139	17	66.0	930	271	81.6	541
Mn	1.35	0.54	0.07	0.510	4.18	1.32	0.537	2.23
Na	6702	1764	178	3050	13453	6690	3855	10709
Rb	8.16	4.55	0.49	1.66	29.4	7.37	3.08	19.3
Sb	0.111	0.072	0.008	0.0047	0.308	0.103	0.0117	0.280
Sc	0.0046	0.0038	0.0008	0.0002	0.0143	0.0042	0.00035	0.0131
Se	2.32	1.29	0.14	0.439	5.80	2.01	0.775	5.65
Sr	4.55	3.22	0.37	0.100	13.7	3.70	0.483	12.3
Zn	105.1	40.1	4.3	7.10	221	104.9	39.2	186
I/Ag	227795	244404	30084	6430	1372273	152078	7184	1006661
I/Br	174	126	14	5.86	576	144	7.61	478
I/Ca	1.43	1.32	0.15	0.136	7.45	1.03	0.151	5.01
I/Cl	0.714	0.540	0.065	0.0274	2.74	0.590	0.174	2.35
I/Co	57499	37571	4428	4911	153211	51491	6458	139428
I/Cr	4017	3212	402	140	17005	3519	367	12607
I/Cu	504	451	57	19.3	2756	395	37.2	1556
I/Fe	10.8	10.3	1.2	0.871	57.9	8.00	1.04	35.8
I/Hg	74076	61725	7598	2000	267834	54512	3962	227350
I/K	0.397	0.334	0.039	0.0209	1.51	0.285	0.0267	1.23
I/Mg	8.53	7.73	0.98	0.551	42.2	6.35	0.756	27.5
I/Mn	1552	1256	161	98.3	7102	1334	209	4672
I/Na	0.288	0.167	0.018	0.0264	0.728	0.252	0.0309	0.650
I/Rb	283	220	25	18.1	998	195	25.7	805
I/Sb	22497	22425	2589	1803	132553	14859	2410	79544
I/Sc	1731401	3207165	735774	65804	13150000	586364	84014	10486000
I/Se	970	821	95	82.9	4361	817	171	3346
I/Sr	1096	2702	335	18.7	20690	411	51.8	4704
I/Zn	20.4	14.4	1.6	1.59	81.5	19.1	2.13	56.4

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 Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn mass fraction (mg/kg, dry mass basis), as well as I/Ag, I/Br, I/Ca, I/Cl, I/ Co, I/Cr, I/Cu, I/Fe, I/Hg, I/K, I/Mg, I/Mn, I/Na, I/Rb, I/Sb, I/Sc, I/Se, I/Sr, and I/Zn mass fraction ratios in normal thyroid.

Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Ag	0.226	0.219	0.031	0.0020	0.874	0.179	0.0022	0.808
Br	412	682	98	3.20	2628	64.5	8.35	2336
Ca	1237	902	138	52.0	4333	1108	116	3536
Cl	8231	3702	772	1757	16786	8326	2543	15157
Co	0.0615	0.0332	0.0046	0.0083	0.159	0.0579	0.0152	0.141
Cr	0.966	0.844	0.121	0.075	3.65	0.673	0.109	2.76
Cu	10.2	9.2	1.7	2.90	35.2	6.0	3.04	34.9
Fe	387	475	56	52,3	2563	188	60.0	1739
Hg	0.924	0.649	0.088	0.0817	3.01	0.856	0.104	2.12
I	991	906	105	29.0	3906	690	84.7	3632
K	6191	2360	352	797	12222	6185	1438	10297
Mg	331	180	26	13.0	844	311	15.0	745
Mn	1.80	1.38	0.21	0.100	5.54	1.45	0.367	5.48
Na	10207	3786	558	2319	22381	9802	3689	16969
Rb	9.16	4.21	0.50	1.00	20.3	8.60	2.48	17.9
Sb	0.137	0.116	0.016	0.0024	0.466	0.101	0.0112	0.423
Sc	0.0144	0.0217	0.0030	0.0002	0.0910	0.0058	0.0002	0.0878
Se	2.75	2.13	0.29	0.720	12.6	2.31	1.05	10.0
Sr	4.48	6.84	0.88	0.42	32.0	1.90	0.769	27.5
Zn	115.3	49.6	5.9	47.0	270	105	48.8	248
I/Ag	26528	60987	8712	412	278870	4507	434	243210
I/Br	29.2	67.0	9.8	0.180	374	5.71	0.280	248
I/Ca	1.86	2.75	0.44	0.0976	12.2	0.792	0.120	9.30
I/Cl	0.141	0.159	0.034	0.0161	0.623	0.0679	0.0191	0.511
I/Co	27066	34081	4869	1333	156580	15037	1954	109476
I/Cr	2811	4364	651	75.5	21693	1151	84.8	16849
I/Cu	211	229	45	9.70	861	104	15.4	812
I/Fe	6.42	7.87	0.96	0.121	39.5	3.21	0.222	27.3
I/Hg	2397	3568	500	133	17703	1203	158	13865
I/K	0.208	0.193	0.030	0.0129	0.793	0.150	0.0156	0.759
I/Mg	12.2	40.3	6.2	0.173	260	2.79	0.223	52.9
I/Mn	1085	1359	212	33.1	5011	549	48.2	4370
I/Na	0.109	0.096	0.015	0.0134	0.418	0.0725	0.0162	0.364
I/Rb	174	226	28	2.16	1336	89.3	5.15	751
I/Sb	22200	48022	6860	281	283613	8174	709	145853
I/Sc	699209	1445465	228548	1767	5705000	137834	5281	5685500
I/Se	502	508	71	16.3	2291	314	43.7	1842
I/Sr	661	774	103	6.85	2782	239	12.9	2389
I/Zn	11.0	12.3	1.5	0.337	66.8	7.10	1.18	42.9

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 Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn mass fraction (mg/kg, dry mass basis), as well as I/Ag, I/Br, I/Ca, I/Cl, I/ Co, I/Cr, I/Cu, I/Fe, I/Hg, I/K, I/Mg, I/Mn, I/Na, I/Rb, I/Sb, I/Sc, I/Se, I/Sr, and I/Zn mass fraction ratios in thyroid benign nodules.

The comparison of our results with published data for the Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, 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)*	Min of means M or M±SD, (n)**	Max of means M or M±SD, (n)**	M±SD
Nomal				
Ag	0.25 (12)	0.000784 (16) [51]	1.20±1.24 (105) [52]	0.015±0.014
Br	18.1 (11)	5.12 (44) [51]	284±44 (14) [53]	14.9±11.0
Ca	1600 (17)	840±240 (10) [54]	3800±320 (29) [54]	1711±1022
Cl	6800 (5)	804±80 (4) [55]	8000 (-) [56]	3400±1452
Co	0.336 (17)	0.026±0.031 (46) [57]	70.4±40.8 (14) [53]	0.040±0.027
Cr	0.69 (17)	0.105 (18) [58]	24.8±2.4 (4) [55]	0.54±0.27
Cu	6.1 (57)	1.42 (120) [59]	220±22 (10) [55]	4.23±1.52
Fe	252 (21)	56 (120) [59]	2444±700 (14) [53]	223±93
Hg	0.08 (13)	0.0008±0.0002 (10) [54]	396±40 (4) [55]	0.042±0.036
I	1888 (95)	159±8 (23) [60]	5772±2708 (50) [61]	1841±1027
K	4400 (17)	46.4±4.8 (4) [55]	6090 (17) [62]	6071±2773
Mg	390 (16)	3.5 (-) [63]	840±400 (14) [64]	285±139
Mn	1.82 (36)	0.44±11 (12) [65]	69.2±7.2 (4) [55]	1.35±0.54
Na	8000 (9)	438 (-) [66]	10000±5000 (11) [64]	6702±1764
Rb	12.3 (9)	≤0.85 (29) [54]	294±191 (14) [53]	8.16±4.55
Sb	0.105 (10)	0.040±0.003 (-) [66]	4.0 (-) [67]	0.11±0.07
Sc	0.009 (4)	0.0018±0.0003 (17) [68]	0.0135±0.0045 (10) [54]	0.005±0.004
Se	2.61 (17)	0.95±0.08 (29) [54]	756±680 (14) [53]	2.32±1.29
Sr	0.73 (9)	0.55±0.26 (21) [58]	46.8±4.8 (4) [55]	4.55±3.22
Zn	118 (51)	32 (120) [59]	820±204 (14) [53]	105±40
TBN				
Ag	0.16 (4)	0.098±0.042 (19) [69]	1.20±2.28 (51) [70]	0.23±0.22
Br	528 (5)	20.2±11.3 (5) [71]	1277 (1) [72]	412±682
Ca	1664 (10)	1080 (2) [71]	8010±1290 (-) [73]	1237±902
Cl	864 (1)	864±84 (4) [55]	864±84 (4) [55]	8231±3702
Co	0.86 (13)	0.110±0.003 (64) [74]	62.8±22.4 (11) [53]	0.062±0.033
Cr	4.0 (6)	0.72 (51) [69]	146±14 (4) [55]	0.97±0.84
Cu	9.84 (38)	0.84 (1) [75]	462 (101) [76]	10.2±9.2
Fe	296 (9)	54.6±36.1 (5) [71]	4848±3056 (11) [53]	387±475
Hg	79.2 (1)	79.2±8.0 (4) [55]	79.2±8.0 (4) [55]	0.92±0.65
I	812 (55)	77±14 (66) [77]	2800 (4) [78]	991±906
K	3100 (6)	72,8±7,2 (4) [55]	6030±620 (-) [73]	6191±2360
Mg	834 (4)	588±388 (13) [79]	1616 (70) [80]	331±180
Mn	2.36 (21)	0.40±0.22 (64) [81]	57.6±6.0 (4) [55]	1.80±1.38
Na	3520 (1)	3520 (25) [82]	3520 (25) [82]	10207±3786
Rb	7.5 (2)	7,0 (10) [68]	864±148 (11) [53]	9.16±4.21
Sb	-	-	-	0.14±0.12
Sc	-	-	-	0.014±0.022
Se	1.97 (9)	0.248 (41) [81]	174±116 (11) [53]	2.75±2.13
Sr	1.64 (3)	1.32 (25) [82]	27.2±2.4 (4) [55]	4.48±6.84
Zn	104 (30)	22.4 (130) [81]	1236±560 (2) [83]	115±50

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

Table 3: Median, minimum and maximum value of means Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, J, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn contents in the normal thyroid 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 Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn mass fraction, as well as between mean values of I/Ag, I/Br, I/Ca, I/Cl, I/ Co, I/Cr, I/Cu, I/Fe, I/Hg, I/K, I/Mg, I/Mn, I/Na, I/Rb, I/Sb, I/Sc, I/Se, 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.

Ratio	Thyroid tissue				Ratio
	Normal thyroid n=105	TBN n=79	Student's t-test *p*	U-test *p*	TBN/NT
Ag	0.0151±0.0016	0.226±0.031	<0.0000001*	<0.01*	15.0
Br	14.9±1.2	412±98	0.00020*	<0.01*	27.7
Ca	1711±109	1237±138	0.0082*	<0.01*	0.72
Cl	3400±174	8231±772	0.0000025*	<0.01*	2.42
Co	0.0399±0.0030	0.0615±0.0046	0.00016*	<0.01*	1.54
Cr	0.539±0.032	0.966±0.121	0.0012*	<0.01*	1.79
Cu	4.23±0.18	10.2±1.7	0.0018*	<0.01*	2.41
Fe	223±10	387±56	0.0055*	<0.01*	1.74
Hg	0.0421±0.0041	0.924±0.088	<0.0000001*	<0.01*	21.9
I	1841±107	991±105	<0.0000001*	<0.01*	0.54
K	6071±306	6191±352	0.798	>0.05	1.02
Mg	285±17	331±26	0.140	>0.05	1.16
Mn	1.35±0.07	1.80±0.21	0.048*	<0.01*	1.33
Na	6702±178	10207±558	<0.0000001*	<0.01*	1.52
Rb	8.16±0.49	9.16±0.50	0.153	>0.05	1.12
Sb	0.111±0.008	0.137±0.016	0.143	>0.05	1.23
Sc	0.0046±0.0008	0.0144±0.0030	0.0054*	<0.01*	3.13
Se	2.32±0.14	2.75±0.29	0.174	>0.05	1.19
Sr	4.55±0.37	4.48±0.88	0.948	>0.05	0.98
Zn	105.1±4.3	115.3±5.9	0.163	>0.05	1.10
I/Ag	227795±30084	26528±8712	<0.00001*	<0.01*	0.12
I/Br	174±14	29.2±9.8	<0.00001*	<0.01*	0.17
I/Ca	1.43±0.15	1.86±0.44	0.367	>0.05	1.30
I/Cl	0.714±0.065	0.141±0.034	<0.00001*	<0.01*	0.20
I/Co	57499±4428	27066±4869	<0.00001*	<0.01*	0.47
I/Cr	4017±402	2811±651	0.119	>0.05	0.70
I/Cu	504±57	211±45	<0.0002*	<0.01*	0.42
I/Fe	10.8±1.2	6.42±0.96	<0.005*	<0.01*	0.59
I/Hg	74076±7598	2397±500	<0.00001*	<0.01*	0.032
I/K	0.397±0.039	0.208±0.030	<0.0003*	<0.01*	0.52
I/Mg	8.53±0.98	12.2±6.2	0.559	>0.05	1.43
I/Mn	1552±161	1085±212	0.083	>0.05	0.70
I/Na	0.288±0.018	0.109±0.015	<0.00001*	<0.01*	0.38
I/Rb	283±25	174±28	<0.004*	<0.01*	0.61
I/Sb	22497±2589	22200±6860	0.968	>0.05	0.99
I/Sc	1731401±735774	699209±228548	0.194	>0.05	0.40
I/Se	970±95	502±71	<0.0002*	<0.01*	0.52
I/Sr	1096±335	661±103	0.218	>0.05	0.60
I/Zn	20.4±1.6	11.0±1.5	<0.00004*	<0.01*	0.54

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

Table 4: Differences between mean values (M±SEM) of Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, J, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn mass fractions, as well as of I/Ag, I/Br, I/Ca, I/Cl, I/ Co, I/Cr, I/Cu, I/Fe, I/Hg, I/K, I/Mg, I/Mn, I/Na, I/Rb, I/Sb, I/Sc, I/Se, I/Sr, 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.

Element	Br	Ca	Cl	Co	Cr	Cu	Fe	Hg	I
Ag	0.13	0.01	-0.17	0.45[c]	0.28[a]	-0.11	-0.01	-0.13	0.01
Br	**1.00**	0.10	-0.08	0.27[a]	0.18	0.24[a]	0,14	-0.14	0.04
Ca	0.10	**1.00**	-0.33[b]	0.30[b]	0.18	-0.24[a]	-0.15	-0.06	0.19
Cl	-0.08	-0.33[b]	**1.00**	-0.38[b]	-0.01	0.22	0.17	0.23	0.11
Co	0.27[a]	0.30[b]	-0.38[b]	**1.00**	0.44[c]	-0.06	0.07	-0.31[b]	0.18
Cr	0.18	0.18	-0.01	0.44[c]	**1.00**	0.06	0.10	-0.32[b]	0.09
Cu	0.24[a]	-0.24[a]	0.22	-0.06	0.06	**1.00**	0.23[a]	0.01	-0.05
Fe	0.14	-0.15	0.17	0.07	0.10	0.23[a]	**1.00**	0.09	-0.24
Hg	-0.14	-0.06	0.22	-0.31[b]	-0.32[b]	0.01	0.09	**1.00**	-0.08
I	0.04	0.19	0.11	0.18	0.09	-0.05	-0.24	-0.08	**1.00**
K	0.10	-0.11	0.43[c]	-0.05	-0.17	-0.12	0.02	0.08	-0.24
Mg	-0.23[a]	0.30[a]	0.18	0.02	-0.03	-0.24[a]	0.06	0.11	-0.14
Mn	0.33[b]	0.08	-0.17	0.18	0.05	-0.06	0.18	0.12	-0.11
Na	-0.07	-0.17	0.46[c]	0.08	0.11	-0.17	0.29[a]	0.07	0.08
Rb	0.27[a]	0.06	-0.10	0.18	0.38[b]	0.20	0.10	-0.01	-0.14
Sb	0.11	0.39[c]	0.41[c]	0.34[b]	0.22	-0.14	-0.07	-0.18	0.37[b]
Sc	-0.28	0.49[a]	-0.38	0.38	0.02	0.16	0.01	-0.29	-0.37
Se	0.05	0.47[c]	-0.26[a]	0.22	0.08	0.03	-0.11	-0.04	0.37[b]
Sr	0.17	0.25[a]	-0.23	0.26[a]	0.20	-0.05	-0.01	-0.09	0.36[b]
Zn	0.09	0.17	-0.13	0.29[a]	0.14	0.23	0.20	0.06	-0.20

Element	K	Mg	Mn	Na	Rb	Sb	Sc	Se	Sr
Ag	0.07	-0.02	-0.08	-0.13	0.03	0.09	0.11	-0.01	0.11
Br	0.10	-0.23[a]	0.33[b]	-0.07	0.27[a]	0.11	-0.28	0.05	0.17
Ca	-0.11	0.30[a]	0.08	-0.17	0.06	0.39[c]	0.49[a]	0.47[c]	0.25[a]
Cl	-0.43[c]	0.18	-0.17	0.46[c]	-0.10	-0.41[c]	-0.38	-0.26[a]	-0.23
Co	-0.05	0.02	0.18	0.08	0.18	0.34[b]	0.38	0.22	0.26[a]
Cr	-0.17	-0.03	0.05	0.11	0.38[b]	0.22	0.02	0.08	0.20
Cu	-0.12	-0.24[a]	-0.06	-0.17	0.20	-0.14	0.16	0.03	-0.05
Fe	0.02	0.06	0.18	0.29[a]	0.10	-0.07	0.01	-0.11	-0.01
Hg	0.08	0.11	0.12	0.07	-0.01	-0.18	-0.29	-0.04	-0.09
I	-0.24	-0.14	-0.11	0.08	-0.14	0.37[b]	-0.37	0.37[b]	0.36[b]
K	**1.00**	0.39[c]	-0.11	0.04	0.21	0.08	-0.12	-0.23[a]	0.06
Mg	0.39[c]	**1.00**	0.02	0.29[a]	0.15	0.21	-0.12	-0.03	0.01
Mn	-0.11	0.02	**1.00**	-0.13	0.05	0.18	0.01	-0.10	0.21
Na	0.04	0.29[a]	-0.13	**1.00**	-0.08	0.08	-0.28	-0.06	-0.10
Rb	0.21	0.15	0.05	-0.08	**1.00**	0.03	0.32	-0.04	0.10
Sb	0.08	0.21	0.18	0.08	0.03	**1.00**	-0.03	0.55[c]	0.19
Sc	-0.12	-0.12	0.01	-0.28	0.32	-0.03	**1.00**	0.32	0.53[a]
Se	-0.23[a]	-0.03	-0.10	-0.06	-0.04	0.55[c]	0.32	**1.00**	0.15
Sr	0.06	0.01	0.21	-0.10	0.10	0.19	0.53[a]	0.15	**1.00**
Zn	0.11	0.16	-0.08	0.05	0.31[b]	0.02	0.21	0.28[a]	0.09

Significant values: [a] $p \le 0.05$, [b] $p \le 0.01$, [c] $p \le 0.001$.

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

Element	Br	Ca	Cl	Co	Cr	Cu	Fe	Hg	I
Ag	0.13	0.01	-0.08	0.45^{c}	0.28^{a}	-0.11	-0.01	-0.13	0.01
Br	**1.00**	0.12	-0.08	0.27^{a}	0.17	0.23	0.14	-0.14	0.04
Ca	0,12	**1.00**	-0.33^{a}	0.32^{a}	0.17	-0.24	-0.14	-0.08	0.19
Cl	-0.08	-0.33^{a}	**1.00**	-0.38^{b}	-0.01	0.22	0.17	0.22	0.11
Co	0. 27^{a}	0.32^{a}	-0.38^{b}	**1.00**	0.44^{b}	-0.06	0.07	-0.31^{a}	0.18
Cr	0.17	0.17	-0.01	0.44^{b}	**1.00**	0.06	0.10	-0.32^{a}	0.09
Cu	0.23	-0.24	0.22	-0.06	0.06	**1.00**	0.23	0.01	-0.05
Fe	0.14	-0.14	0.17	0.07	0.10	0.23	**1.00**	0.09	-0.24
Hg	-0.14	-0.08	0.22	-0.31^{a}	-0.32^{a}	0.01	0.09	**1.00**	-0.08
I	0.04	0.19	0.11	0.18	0.09	-0.05	-0.24	-0.08	**1.00**
K	0.10	-0.13	-0.43^{b}	-0.05	-0.16	-0.12	0.02	0.08	-0.24
Mg	-0.23	0.27^{a}	0.18	0.02	-0.03	-0.24	0.06	0.11	-0.14
Mn	0.33^{a}	0.08	-0.17	0.18	0.05	-0.06	0.18	0.12	-0.11
Na	-0.07	-0.14	0.46^{c}	0.08	0.11	-0.17	0.29^{a}	0.07	0.08
Rb	0.27^{a}	0.06	-0.10	0.15	0.36^{b}	0.21	0.08	0.01	-0.14
Sb	0.11	0.38^{b}	-0.41^{b}	0.33^{a}	0.22	-0.14	-0.07	-0.18	0.37^{b}
Sc	-0.28	0.49^{b}	-0.38^{a}	0.38^{a}	0.02	0.16	0.01	-0.29	0.37^{a}
Se	0.05	0.47^{c}	-0.26	0.22	0.08	0.03	-0.11	-0.04	0.36^{b}
Sr	0.17	0.25	-0.23	0.26	0.19	-0.05	-0.01	-0.09	-0.20
Zn	0.09	0.18	-0.13	0.29^{a}	0.14	0.23	0.19	0.06	0.01

Element	K	Mg	Mn	Na	Rb	Sb	Sc	Se	Sr
Ag	0.07	-0.01	-0.08	0.18	-0.05	0.09	0.11	-0.01	0.11
Br	0.10	-0.23	0.33^{a}	-0.07	0.27^{a}	0.11	-0.28	0.05	0.17
Ca	-0.13	0.27^{a}	0.08	-0.14	0.06	0.38^{b}	0.49^{b}	0.47^{c}	0.25
Cl	-0.43^{b}	0.18	-0.17	0.46^{c}	-0.10	-0.41^{b}	-0. 38^{a}	-0.26	-0.23
Co	-0.05	0.02	0.18	0.08	0.15	0.33^{a}	0. 38^{a}	0.22	0.26
Cr	-0.16	-0.03	0.05	0.11	0.36^{b}	0.22	0.02	0.08	0.19
Cu	-0.12	-0.24	-0.06	-0.17	0.21	-0.14	0.16	0.03	-0.05
Fe	0.02	0.06	0.18	0.29^{a}	0.08	-0.07	0.01	-0.11	-0.01
Hg	0.08	0.11	0.12	0.07	0.01	-0.18	-0.29	-0.04	-0.09
I	-0.24	-0.14	-0.11	0.08	-0.14	0.37^{b}	-0. 37^{a}	0.36^{b}	-0.20
K	**1.00**	0.39^{b}	-0.11	0.04	0.20	0.08	-0.12	-0.23	0.06
Mg	0.39^{b}	**1.00**	0.02	0.29^{a}	0.12	0.21	-0.12	-0.02	0.01
Mn	-0.11	0.02	**1.00**	-0.13	0.03	0.18	0.01	-0.10	0.21
Na	0.04	0.29^{a}	-0.13	**1.00**	-0.14	0.08	-0.28	-0.06	-0.10
Rb	0.20	0.12	0.03	-0.14	**1.00**	0.04	0.32^{a}	-0.03	0.09
Sb	0.08	0.21	0.18	0.08	0.04	**1.00**	-0.03	0.55^{c}	0.19
Sc	-0.12	-0.12	0.01	-0.28	0.32^{a}	-0.03	**1.00**	0.32a	0.53^{c}
Se	-0.23	-0.02	-0.10	-0.06	-0.03	0.55^{c}	0.32	**1.00**	0.14
Sr	0.06	0.01	0.21	-0.10	0.09	0.19	0.53^{c}	0.14	**1.00**
Zn	0.11	0.16	-0.08	0.05	0.30^{a}	0.02	0.21	0.28^{a}	0.09

Significant values: ^{a} $p \leq 0.05$, ^{b} $p \leq 0.01$, ^{c} $p \leq 0.001$.

Table 6: Intercorrelations of the chemical element mass fraction 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/Ag	I/Br	I/Ca	I/Cl	I/Co	I/Cr	I/Cu	I/Fe	I/Hg
I/Ag	**1.00**	0.23	0.19	0.29[a]	0.32[b]	0.35[b]	0.12	0.01	0.13
I/Br	0.23	**1.00**	0.29[a]	0.29[a]	0.54[c]	0.60[c]	0.27[a]	0.36[b]	0.03
I/Ca	0.19	0.29[a]	**1.00**	0.08	0.61[c]	0.53[c]	0.28[a]	0.46[c]	0.33[b]
I/Cl	0.29[a]	0.29[a]	0.08	**1.00**	0.13	0.35[b]	0.32[a]	0.38[b]	0.57[c]
I/Co	0.32[b]	0.54[c]	0.61[c]	0.13	**1.00**	0.55[c]	0.37[b]	0.45[c]	0.22
I/Cr	0.35[b]	0.60[c]	0.53[c]	0.35[b]	0.55[c]	**1.00**	0.34[b]	0.45[c]	0.25[a]
I/Cu	0.12	0.27[a]	0.28[a]	0.32[a]	0.37[b]	0.34[b]	**1.00**	0.43[c]	0.27[a]
I/Fe	0.01	0.36[b]	0.46[c]	0.38[b]	0.45[c]	0.45[c]	0.43[c]	**1.00**	0.58[c]
I/Hg	0.13	0.03	0.33[b]	0.57[c]	0.22	0.25[a]	0.27[a]	0.58[c]	**1.00**
I/K	0.13	0.40[c]	0.53[c]	0.30[a]	0.52[c]	0.57[c]	0.44[c]	0.67[c]	0.51[c]
I/Mg	0.28[a]	0.25[a]	0.56[c]	0.58[c]	0.64[c]	0.71[c]	0.31[b]	0.40[c]	0.43[c]
I/Mn	0.46[c]	0.36[b]	0.68[c]	0.40[c]	0.61[c]	0.58[c]	0.37[b]	0.58[c]	0.49[c]
I/Na	0.16	0.49[c]	0.47[c]	0.76[c]	0.52[c]	0.66[c]	0.50[c]	0.65[c]	0.62[c]
I/Rb	0.31[a]	0.48[c]	0.52[c]	0.43[c]	0.62[c]	0.65[c]	0.53[c]	0.64[c]	0.46[c]
I/Sb	0.22	0.40[c]	0.42[c]	-0.07	0.34[b]	0.40[c]	0.06	0.09	-0.10
I/Sc	-0.19	-0.08	0.39	0.34	-0.04	0.31	0.21	0.36	0.36
ISe	0.03	0.29[a]	0.61[c]	0.10	0.42[c]	0.39[b]	0.36[b]	0.31[a]	0.37[b]
I/Sr	0.01	0.09	0.15	0.40[c]	0.08	0.30[a]	0.11	0.18	0.33[b]
I/Zn	0.11	0.34[b]	0.64[c]	0.35[b]	0.60[c]	0.45[c]	0.61[c]	0.54[c]	0.49[c]

Ratio	I/K	I/Mg	I/Mn	I/Na	I/Rb	I/Sb	I/Sc	I/Se	I/Sr
I/Ag	0.13	0.28[a]	0.46[c]	0.16	0.31[a]	0.22	-0.19	0.03	0.01
I/Br	0.40[c]	0.25[a]	0.36[b]	0.49[c]	0.48[c]	0.40[c]	-0.08	0.29[a]	0.09
I/Ca	0.53[c]	0.56[c]	0.68[c]	0.47[c]	0.52[c]	0.42[c]	0.39	0.61[c]	0.15
I/Cl	0.30[a]	0.58[c]	0.40[c]	0.76[c]	0.43[c]	-0.07	0.34	0.10	0.40[c]
I/Co	0.52[c]	0.64[c]	0.61[c]	0.52[c]	0.62[c]	0.34[b]	-0.04	0.42[c]	0.08
I/Cr	0.57[c]	0.71[c]	0.58[c]	0.66[c]	0.65[c]	0.40[c]	0.31	0.39[b]	0.30[a]
I/Cu	0.44[c]	0.31[b]	0.37[b]	0.50[c]	0.53[c]	0.06	0.21	0.36[b]	0.11
I/Fe	0.67[c]	0.40[c]	0.58[c]	0.65[c]	0.64[c]	0.09	0.36	0.31[a]	0.18
I/Hg	0.51[c]	0.43[c]	0.49[c]	0.62[c]	0.46[c]	-0.10	0.36	0.37[b]	0.33[b]
I/K	**1.00**	0.71[c]	0.55[c]	0.76[c]	0.79[c]	0.17	0.08	0.40[c]	0.07
I/Mg	0.71[c]	**1.00**	0.53[c]	0.68[c]	0.67[c]	0.24	0.11	0.42[c]	0.52[c]
I/Mn	0.55[c]	0.53[c]	**1.00**	0.57[c]	0.73[c]	0.35[b]	-0.01	0.39[b]	0.51[c]
I/Na	0.76[c]	0.68[c]	0.57[c]	**1.00**	0.70[c]	0.22	0.20	0.52[c]	0.31[a]
I/Rb	0.79[c]	0.67[c]	0.73[c]	0.70[c]	**1.00**	0.23	0.52[a]	0.38[b]	0.12
I/Sb	0.17	0.24	0.35[b]	0.22	0.23	**1.00**	0.15	0.43[c]	0.08
I/Sc	0.08	0.11	-0.01	0.20	0.52[a]	0.15	**1.00**	0.33[b]	0.55[c]
ISe	0.40[c]	0.42[c]	0.39[b]	0.52[c]	0.38[b]	0.43[c]	0.33[b]	**1.00**	0.16
I/Sr	0.07	0.52[c]	0.51[c]	0.31[a]	0.12	0.08	0.55[c]	0.16	**1.00**
I/Zn	0.64[c]	0.63[c]	0.50[c]	0.67[c]	0.71c	0.14	0.36[b]	0.56[c]	0.20

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/Ag	I/Br	I/Ca	I/Cl	I/Co	I/Cr	I/Cu	I/Fe	I/Hg
I/Ag	**1.00**	0.61^{c}	0.33^{a}	0.38^{b}	0.49^{c}	0.01	0.52^{c}	0.42^{b}	0.33^{a}
I/Br	0.61^{c}	**1.00**	0.14	0.76^{c}	0.57^{c}	0.27	0.72^{c}	0.43^{b}	0.05
I/Ca	0.33^{a}	0.14	**1.00**	0.84^{c}	0.46^{b}	0.28	0.15	0.67^{c}	0.23
I/Cl	0.38^{b}	0.76^{c}	0.84^{c}	**1.00**	0.67^{c}	0.86^{c}	0.28	0.67^{c}	0.60^{b}
I/Co	0.49^{c}	0.57^{c}	0.46^{b}	0.67^{c}	**1.00**	0.26	0.82^{c}	0.59^{c}	0.37^{b}
I/Cr	0.01	0.27	0.28	0.86^{c}	0.26	**1.00**	0.30	0.52^{c}	0.21
I/Cu	0.52^{c}	0.72^{c}	0.15	0.28	0.82^{c}	0.30	**1.00**	0.43^{a}	0.34
I/Fe	0.42^{b}	0.43^{b}	0.67^{c}	0.67^{c}	0.59^{c}	0.52^{c}	0.43^{a}	**1.00**	0.75^{c}
I/Hg	0.33^{a}	0.05	0.23	0.60^{b}	0.37^{b}	0.21	0.34	0.75^{c}	**1.00**
I/K	0.58^{c}	0.67^{c}	0.59^{c}	0.83^{c}	0.68^{c}	0.30^{a}	0.74^{c}	0.65^{c}	0.37^{b}
I/Mg	0.33^{a}	0.10	0.64^{c}	0.41	0.34^{a}	0.14	-0.05	0.67^{c}	0.23
I/Mn	0.53^{c}	0.44^{b}	0.39^{a}	0.51^{a}	0.58^{c}	0.10	0.84^{c}	0.27	0.26
I/Na	0.54^{c}	0.67^{c}	0.66^{c}	0.98^{c}	0.64^{c}	0.40^{b}	0.74^{c}	0.57^{c}	0.27^{a}
I/Rb	0.68^{c}	0.71^{c}	0.42^{b}	0.90^{c}	0.60^{c}	0.23	0.64^{c}	0.61^{c}	0.37^{b}
I/Sb	0.34^{a}	0.19	0.16	0.32	0.31^{a}	0.02	0.57^{b}	0.32^{a}	0.36^{b}
I/Sc	-0.11	0.71^{c}	0.34^{a}	0.15	0.26	-0.03	0.21	0.08	0.13
ISe	0.43^{b}	0.75^{c}	0.52^{c}	0.79^{c}	0.71^{c}	0.51^{c}	0.70^{c}	0.54^{c}	0.16
I/Sr	0.13	0.02	0.54^{c}	0.76^{c}	0.61^{c}	0.53^{c}	0.54^{b}	0.48^{b}	0.21
I/Zn	0.54^{c}	0.81^{c}	0.47^{b}	0.85^{c}	0.72^{c}	0.28	0.75^{c}	0.57^{c}	0.12

Ratio	I/K	I/Mg	I/Mn	I/Na	I/Rb	I/Sb	I/Sc	I/Se	I/Sr
I/Ag	0.58^{c}	0.33^{a}	0.53^{c}	0.54^{c}	0.68^{c}	0.34^{a}	-0.11	0.43^{b}	0.13
I/Br	0.67^{c}	0.10	0.44^{b}	0.67^{c}	0.71^{c}	0.19	0.71^{c}	0.75^{c}	0.02
I/Ca	0.59^{c}	0.64^{c}	0.39^{a}	0.66^{c}	0.42^{b}	0.16	0.34^{a}	0.52^{c}	0.54^{c}
I/Cl	0.83^{c}	0.41	0.51^{a}	0.98^{c}	0.90^{c}	0.32	0.15	0.79^{c}	0.76^{c}
I/Co	0.68^{c}	0.34^{a}	0.58^{c}	0.64^{c}	0.60^{c}	0.31^{a}	0.26	0.71^{c}	0.61^{c}
I/Cr	0.30^{a}	0.14	0.10	0.40^{b}	0.23	0.02	-0.03	0.51^{c}	0.53^{c}
I/Cu	0.74^{c}	-0.05	0.84^{c}	0.74^{c}	0.64^{c}	0.57^{b}	0.21	0.70^{c}	0.54^{b}
I/Fe	0.65^{c}	0.67^{c}	0.27	0.57^{c}	0.61^{c}	0.32^{a}	0.08	0.54^{c}	0.48^{b}
I/Hg	0.37^{b}	0.23	0.26	0.27^{a}	0.37^{b}	0.36^{b}	0.13	0.16	0.21
I/K	**1.00**	0.34^{a}	0.57^{c}	0.88^{c}	0.85^{c}	0.43^{b}	-0.01	0.85^{b}	0.47^{b}
I/Mg	0.34^{a}	**1.00**	-0.02	0.32^{a}	0.20	0.06	0.70^{c}	0.39^{b}	0.31^{a}
I/Mn	0.57^{c}	-0.02	**1.00**	0.64^{c}	0.61^{c}	0.46^{b}	0.12	0.50^{c}	0.39^{b}
I/Na	0.88^{c}	0.32^{a}	0.64^{c}	**1.00**	0.82^{c}	0.38^{b}	0.04	0.85^{c}	0.54^{c}
I/Rb	0.85^{c}	0.20	0.61^{c}	0.82^{c}	**1.00**	0.29^{a}	0.10	0.70^{c}	0.30^{a}
I/Sb	0.43^{b}	0.06	0.46^{b}	0.38^{b}	0.29^{a}	**1.00**	0.34^{a}	0.11	0.34^{a}
I/Sc	-0.01	0.70^{c}	0.12	0.04	0.10	0.34^{a}	**1.00**	0.03	0.31^{a}
I/Se	0.85^{b}	0.39^{b}	0.50^{c}	0.85^{c}	0.70^{c}	0.11	0.03	**1.00**	0.50^{c}
I/Sr	0.47^{b}	0.31^{a}	0.39^{b}	0.54^{c}	0.30^{a}	0.34^{a}	0.31^{a}	0.50^{c}	**1.00**
I/Zn	0.84^{c}	0.32^{a}	0.58^{c}	0.87^{c}	0.85^{c}	0.19	0.13	0.84^{c}	0.35^{a}

r

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).

4. Discussion

4.1. Precision and accuracy of results

Previously found good agreement of the Ag, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn contents in CRM IAEA H-4 (animal muscle) and IAEA HH-1 (human hair) samples determined by EDXRF, INAA-SLR, and INAA-LLR with the certified data of these CRMs [25-30} 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 Ag, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn, as well as I/Ag, I/Br, I/Ca, I/Cl, I/ Co, I/Cr, I/Cu, I/Fe, I/Hg, I/K, I/Mg, I/Mn, I/Na, I/Rb, I/Sb, I/Sc, I/Se, I/Sr, 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.

4.2. Comparison with published data

The obtained means for Br, Ca, Cl, Cr, Cu, Fe, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, 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 [51-68]. The obtained mean for Ag and Co were two orders of magnitude lower the median of previously reported data, but they were inside the range of previously reported means.

Ag, Co

In TBN tissues (Table 3) our results were comparable with published data for Al, Br, Ca, Cr, Cu, Fe, I, Mn, Rb, Se, Sr, and Zn contents [53,55,59,68-73,75-78,81-83]. Our mean of K content was outside the range of published means [55,73], 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 [79,80]. 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 2.9 times higher, respectively, than the only reported result [55] and [82], respectively. Obtained means for Co and Hg were almost one and two orders of magnitude, respectively, lower the median of previously reported data [53,55,74]. No published data referring Sb and Sc 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%) [57] and ash (4.16% on dry mass basis) [84] contents in thyroid of adults.

No published data referring to I/Ag, I/Br, I/Ca, I/Cl, I/ Co, I/Cr, I/Cu, I/Fe, I/Hg, I/K, I/Mg, I/Mn, I/Na, I/Rb, I/Sb, I/Sc, I/Se, I/Sr, 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 [85-90].

The range of means of Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, 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 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 [91-93].

4.3. 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 Ag, Br, Cl, Co, Cr, Cu, Fe, Hg, Mn, Na, and Sc were 15.0, 27.7, 2.4, 1.5, 1.8, 2.4, 1.7, 21.9, 1.3, 1.5, and 3.1 times, respectively, higher whereas mass fractions of Ca and I were 28% and 46% , respectively, lower than in normal tissues of the thyroid. Since the changes in the content Ag, Br, Cl, Co, Cu, Fe, Hg, and Na, on the one hand, and I, on the other hand, in TBN were in different directions, the I/Ag, I/Br, I/Cl, I/Co, I/Cu, I/Fe, I/Hg, and I/Na ratios in TBN also differed significantly from the norm (Table 4). Moreover, the I/K, I/Rb, I/Se, and I/Zn mass fraction ratios in TBN was 48%, 39%, $8%, and 46%, 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.

4.4. 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 Sb, I and Se, and also I and Sr (Table 5). In TBN, the correlations I-Sb and I-Se were preserved, the correlation between I and Sr disappeared, but a correlation between I and Sc was found. (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 Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, 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 Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn in the normal thyroid gland and TBN are interrelated and depend on the content of I.

5. Conclusion

In this work, ChEs analyses were carried out in the tissue samples of normal thyroid and TBN using the combination of nondestructive nuclear methods. It was shown that the combination of three methods such as EDXRF, INAA-SLR and INAA-LLR is a useful analytical tool for determining the content of ChEs in thyroid tissue samples, including core biopsy. This method allows determine content of Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, and Zn (twenty ChEs), Our data reveal that in TBN the mass fraction of Ag, Br, Cl, Co, Cr, Cu, Fe, Hg, Mn, Na, and Sc 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/Ag, I/Br, I/Cl, I/Co, I/Cu, I/Fe, I/Hg, I/K, I/Na, I/Rb, I/Se, 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 Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, 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, such ChEs as Ag, Br, Ca, Cl, Co, Cr, Cu, Fe, Hg, I, K, Mg, Mn, Na, Rb, Sb, Sc, Se, Sr, 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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