Original Research Article

COMPARISON OF TWENTY CHEMICAL ELEMENT CONTENTS IN NORMAL AND GOITROUS THYROID

ABSTRACT

Background: Nodular goiter (NG) is an internationally important health problem. The aim of this exploratory study was to evaluate whether significantchanges in the thyroid tissue levels of twenty chemical elements (ChE) Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn exist in the goitrous transformed thyroid.

Methods: Thyroid tissue levels of twenty ChEwere prospectively evaluated in 46 patients with NG and 105 healthy inhabitants. Measurements were performed using a combination of non-destructive and destructive methods: instrumental neutron activation analysis and inductively coupled plasma atomic emission spectrometry, respectively. Tissue samples were divided into two portions. One was used for morphological study while the other was intended for ChE analysis.

Results: It was found that contents of Al, B, Br, Cl, Cu, Fe, Li, Mg, Mn, Na, P, S, Si, V, and Zn are significantly higher whereas the levels of I some lowerin NG than in normal tissues.

Conclusion: There are considerable changes in ChE contents in the goitrous tissue of thyroid.

Keywords: Thyroid nodular goiter; Intact thyroid; Chemical elements; Biomarkers for goiter diagnosis; Instrumentalneutron activation analysis; Inductively coupled plasma atomic emission spectrometry.

INTRODUCTION

No less than 10 % of the world population is affected by goiter detected during the examination and palpation and most of these thyroidal lesions are nodular goiters (NG) [1]. However, using ultrasonography NG can be detected in almost 70% of the general population [2]. NG is also known as endemic nodular goitre, simple goitre, nodular hyperplasia, nontoxic uninodulargoitre or multinodular goiter [3]. NG is benign lesions; however, during clinical examination, they can mimic malignant tumors. NG can be hyperfunctioning, hypofunctioning, and normal functioning. EuthyroidNG is defined as a local enlargement of thyroid without accompanying disturbance in thyroid function [3].

For over 20th century, there was the dominant opinion that NG is the simple consequence of iodine (I) deficiency. However, it was found that NG is a frequent disease even in those countries and regions where the population is never exposed to I shortage [4]. Moreover, it was shown that I excess has severe consequences on human health and associated with the presence of thyroidal disfunctions and autoimmunity, NG and diffuse goiter, benign and malignant tumors of gland [5-8]. It was also demonstrated that besides the I deficiency and excess many other dietary, environmental, and occupational factors are associated with the NG incidence [9-11]. Among them a disturbance of evolutionary stable input of many chemical elements (ChE) in human body after industrial revolution plays a significant role in etiology of thyroidal disorders [12].

Besides I involved in thyroid function, other ChE have also essential physiological functions such as maintenance and regulation of cell function, gene regulation, activation or inhibition of enzymatic reactions, and regulation of membrane function [13]. Essential or toxic (goitrogenic, mutagenic, carcinogenic) properties of ChE depend on tissue-specific need or tolerance, respectively [13].Excessive accumulation or an imbalance of the ChE may disturb the cell functions and may result in cellular degeneration, death, benign or malignant transformation [13-15].

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

To date, the pathogenesis of NG has to be considered as multifactorial. The present study was performed to clarify the role of twenty ChE in the maintenance of thyroid growth and goitrogenesis. Having this in mind, our aim was to assess the aluminum (Al), boron (B), barium (Ba), bromine (Br), calcium (Ca), chlorine (Cl), coper (Cu), iron (Fe), I, potassium (K), lithium (Li), magnesium (Mg), manganese (Mn), sodium (Na), phosphorus (P), sulfur (S), silicon (Si), strontium (Sr), vanadium (V), and zinc (Zn) mass fraction contents in NG tissue using a combination of non-destructive and destructive methods: instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR) and inductively coupled plasma atomic emission spectrometry (ICPAES), respectively. A further aim was to compare the levels of these twenty ChE in the goitrous thyroid with those in normal gland of apparently healthy persons.

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/ornational research committee and with the 1964 Helsinki declaration and its later amendments, or with comparable ethical standards.

MATERIALS AND METHODS

Samples

All patients suffered from NG (n=46, mean age M±SD was 48±12 years, range 30-64) were hospitalized in the Head and Neck Department of the Medical Radiological Research Centre. Thick-needle puncture biopsy of suspicious nodules of the thyroid was performed for every patient, to permit morphological study of thyroid tissue at these sites and to estimate their ChE contents. For all patients the diagnosis has been confirmed by clinical and morphological results obtained during studies of biopsy and resected materials. Histological conclusion for all thyroidal lesions was the colloid NG.

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. Samples were obtained within 48 hours after a sudden death. The majority of deaths were due to trauma. 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.

Sample preparation, instrumentation and analytical methods

All tissue samples were divided into two portions using a titanium scalpel[48]. One was used for morphological study while the other was intended for ChE analysis. After the samples intended for ChE analysis were weighed, they were freeze-dried and homogenized[49].

The pounded samples weighing about 5-10 mg (for biopsy) and 100 mg (for resected materials) were used for ChE measurement by INAA-SLR. The samples for INAA-SLR were sealed separately in thin polyethylene films washed beforehand with acetone and rectified alcohol. The sealed samples were placed in labeled polyethylene ampoules. 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). Thyroid samples irradiated by neutrons were measured using a gamma spectrometer. The gamma spectrometer included the 98 cm^3Ge(Li) detector with on-line computer-based multichannel analyzer system (NUC 8100, Hungary) and provided a resolution of 1.9 keV on the ^{60}Co 1332 keV line.

After INAA-SLR investigation the thyroid samples were taken out from the polyethylene ampoules and used for ICP-AES. The samples were decomposed in autoclaves. For this 1.5 mL of concentrated HNO_3 (nitric acid at 65 %, maximum (max) of 0.0000005 % Hg; GR, ISO, Merck, Darmstadt, Germany) and 0.3 mL of H_2O_2 (pure for analysis) were added to each thyroid samples, which were placed in one-chamber autoclaves (Ancon-AT2, Ltd., Moscow, Russia) and then heated for 3 h at 160–200 °C. After autoclaving, they were cooled to room temperature and solutions from the decomposed samples were diluted with deionized water (up to 20 mL) and transferred to plastic measuring bottles. Simultaneously, the same procedure was performed in autoclaves without tissue samples (containing only HNO_3+H_2O_2+ deionized water), and the resultant solutions were used as control samples. Sample aliquots 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 by ICP-AES 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 ChE content 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 were presented in our earlier publications concerning chemical element contents in human thyroid, scalp hair, and prostate[33,34,50-55].

Standards and Certified Reference Material

To determine contents of the ChE by comparison with a known standard, biological synthetic standards (BSS) prepared from phenol-formaldehyde resins were used[56].In addition to BSS, aliquots of commercial, chemically pure compounds were also used as standards. Ten sub-samples of certified reference material (CRM) IAEA H-4 (animal muscle) and five sub-samples of CRM of the Institute of Nuclear Chemistry and Technology (INCT, Warszawa, Poland) INCT-SBF-4 Soya Bean Flour, INCT-TL-1 Tea Leaves, and INCT-MPH-2Mixed Polish Herbs were treated and analyzed in the same conditions that thyroid samples to estimate the precision and accuracy of results.

Computer programs and statistic

A dedicated computer program for INAA mode optimization was used[57]. All thyroid samples were prepared in duplicate, and mean values of ChE contents were used. Mean values of ChE contents were used in final calculation for the Br, Fe, Rb, and Zn mass fractions measured by two methods. Using Microsoft Office Excel, a summary of the statistics, including, arithmetic mean, standard deviation, standard error of mean, minimum and maximum values, median, percentiles with 0.025 and 0.975 levels was calculated for ChE contents. The difference in the results between two groups (normal and NG) was evaluated by the parametric Student's *t*-test and non-parametric Wilcoxon-Mann-Whitney *U*-test.

RESULTS

Table 1 depicts our data for Br, Ca, Cl, K, Mg, Mn, and Na mass fractions in ten sub-samples of CRM IAEA H-4 (animal muscle) certified reference material and the certified values of this material.

Table 1: INAA-SLR data of chemical element contents in the IAEA H-4 (animal muscle) reference material compared to certified values (mg/kg on dry mass basis)

Element	Certified values			This work results
	Mean	95% confidence interval	Type	Mean±SD
Br	4.1	3.5 – 4.7	C	5.0±0.9
Ca	188	163 – 213	C	238±59
Cl	1890	1810 – 1970	C	1950±230
K	15800	15300 – 16400	C	16200±3800
Mg	1050	990 – 1110	C	1100±190
Mn	0.52	0.48 – 0.55	N	0.55±0.11
Na	2060	1930 – 2180	C	2190±140

Mean - arithmetical mean, SD - standard deviation, C - certified values, N - non-certified values

Table 2 presents our data for Al, B, Ba, Ca, Cu, Fe, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fractions in five sub-samples of INCT-SBF-4 Soya Bean Flour, INCT-TL-1 Tea Leaves and INCT-MPH-2Mixed Polish Herbs certified reference materials and the certified (or informative) values of this material.

Table 2:ICP-AES data of chemical element contents in Certified Reference Materials (M±SD, mg/kg on dry mass basis)

Element	Soya Bean Flour (INCT-SBF-4)		Tea Leaves (INCT-TL-1)		Mixed Polish Herbs (INCT-MPH-2)	
	Certificate	This work result	Certificate	This work result	Certificate	This work result
Al	45.5±3.7	37.1±1.4	2290±280	2248±61	670±111	485±79
B	39.9±4.0	34.5±1.4	26[a]	24.8±1.2	-	28.8±8.1
Ba	7.30±0.23	7.38±0.23	43.2±3.9	44.7±2.6	32.5±2.5	32.2±0.6
Ca	2467±170	2737±190	5820±520	6296±360	10800±700	10250±294
Cu	14.3±0.5	14.2±0.8	20.4±1.5	19.7±1.1	7.77±0.53	8.28±0.47
Fe	90.8±4.0	80.5±6.9	432[a]	493±39	460[a]	459±33
K	24230±830	25230±1090	17000±1200	17810±1320	19100±1200	20280±870
Li	-	0.0047±0.0018	-	0.217±0.034	-	0.574±0.044
Mg	3005±82	2983±340	2240±170	2415±115	2920±180	2955±159
Mn	32.3±1.1	30.0±1.0	1570±110	1628±145	191±12	197±5
Na	-	10.2±3.4	24.7±3.2	24.2±3.5	350[a]	338±17
P	6555±355	6782±248	1800[a]	2457±150	2500[a]	3022±481
S	4245±471	4468±529	2470±250	2500±230	2410±140	2409±159
Si	-	26.7±4.8	-	325±34	-	268±64
Sr	9.32±0.46	8.76±0.21	20.8±1.7	19.8±1.0	37.6±2.7	37.4±2.1
V	-	≤0.22	2.0±0.4	1.8±0.2	0.95±0.16	0.90±0.04
Zn	52.3±1.3	54.8±6.6	34.7±2.7	36.0±3.7	33.5±2.1	32.0±6.1

M - arithmetic mean, SD - standard deviation, [a] Informative values

The comparison of our results for the Ca, K, Mg, Mn, and Na mass fractions (mg/kg, dry mass basis) in the normal human thyroid obtained by both INAA-SLR and ICP-AES methods is shown in Table 3.

Table 3: Comparison of the mean values (M±SEM) of the chemical element mass fractions (mg/kg, on dry-mass basis)in the normal human thyroid (males and females combined) obtained by both NAA-SLR and ICP-AES methods

Element	NAA-SLR (M_1)	ICP-AES (M_2)	Δ, %
Ca	1692±109	1633±108	3.5

K	6071±306	6764±298	-11.4
Mg	285±17	308±17	-8.1
Mn	1.35±0.07	1.21±0.07	10.4
Na	6702±178	7154±201	-6.7

M – arithmetic mean, SEM – standard error of mean, $\Delta=[(M_1 - M_2)/M_1]\cdot 100\%$.

Table 4 presents certain statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, percentiles with 0.025 and 0.975 levels) of the Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fraction in normal and goitrous thyroid.

The comparison of our results with published data for Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn mass fraction in normal and goitrous thyroid[58-91] is shown in Table 5.

The ratios of means and the difference 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 fractions in normal and goitrous thyroid are presented in Table 6.

DISCUSSION

Precision and accuracy of results

A good agreement of our results for the Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Mg, Mn, Na, P, S, Sr, V, and Zn mass fractions with the certified values of CRM IAEA H-4, INCT-SBF-4, INCT-TL-1, and INCT-MPH-2 (Tables 1 and 2) as well as the similarity of the means of the Ca, K, Mg, Mn, and Na mass fractions in the normal human thyroid determined by both INAA-SLR and ICP-AES methods (Table 3) demonstrates an acceptable precision and accuracy of the results obtained in the study and presented in Tables 4-6.

The mean values and all selected statistical parameters were calculated for twenty ChE (Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn) mass fractions (Table 4). The mass fraction of Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn were measured in all, or a major portion of normal and goitrous tissue samples.

Comparison with published data

The means obtained 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 5, agree 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. The mean obtained for Li is two orders of magnitude lower than the median of previously reported data. Moreover, it is outside the range of previously reported means. A number of values for ChE mass fractions were not expressed on a dry mass basis by the authors of the cited references. Hence we calculated these values using published data for water 75%[92] and ash 4.16% on dry mass basis[93] contents in thyroid of adults.

In goitrous tissues our results for Al, Br, Ca, Cu, Fe, I, Mn, Si, and Zncontents were within the range of published means, while means for K and Sr were some higher median of previously reported means and also higher the upper level of the range of these means (Table 5). Only one published article on Ba [80], Na [59], P [88], S [88], Si [88], and V [80] contents in the goitroustissue samples was found in the literature. The mean obtained in the present study for S content in the goitroustissue agreed well with early published data, while means for Ba and P were some lower and the mean for Na was some higher. The obtained mean for V content in the goitrous tissue was more than one order of magnitude lower than the only reported result. No published data referring B, Cl, and Li contents of goitrous thyroid tissue were found.

Table 4: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) in normal and goitrous thyroid

Tissue	Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Normal	Al	10.5	13.4	1.8	0.800	69.3	6.35	1.19	52.9
n=105	B	0.476	0.434	0.058	0.200	2.30	0.300	0.200	1.73
	Ba	1.12	1.15	0.15	0.0480	5.00	0.680	0.0838	4.48
	Br	14.9	11.0	1.2	1.90	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	0.500	7.15	4.10	1.57	6.41
	Fe	223	95	10	52.0	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	66.0	930	284	95.8	541
	Mn	1.28	0.56	0.07	0.470	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	5.70	180	36.0	7.11	174
	Sr	3.81	2.93	0.34	0.100	12.6	2.90	0.365	11.3
	V	0.102	0.039	0.005	0.0200	0.250	0.100	0.0440	0.192
	Zn	94.8	39.6	4.2	7.10	215	88.5	34.9	196
Goiter	Al	27.1	24.7	5.3	6.60	95.1	20.5	6.92	85.2
n=46	B	1.71	1.19	0.26	0.90	5.00	1.00	0.95	5.00
	Ba	1.43	1.75	0.37	0.18	8.20	0.96	0.238	5.79
	Br	36.3	31.3	6.99	8.0	131	26.6	8.95	110
	Ca	1422	834	164	288	4333	1272	362	3219
	Cl	9117	3866	1223	4226	16786	8259	4504	15869
	Cu	8.51	7.15	1.60	2.90	34.8	5.95	3.00	26.2
	Fe	337	321	51	62.0	1350	199	65.0	1214
	I	1310	1433	221	29.0	8260	974	107	3713
	K	6610	2233	430	3353	12222	6110	3395	10984
	Li	0.0281	.0.0117	0.0030	0.0073	0.0541	0.0259	0.0089	0.0530
	Mg	356	119	23	63.0	612	371	149	559
	Mn	1.77	1.13	0.23	0.450	5.50	1.60	0.516	4.12
	Na	11782	4342	836	7229	28481	10697	7279	20921
	P	5181	1798	383	2890	9637	5030	2919	8827
	S	10961	2091	446	5591	14970	10719	6824	14579
	Si	81.3	57.3	12.5	7.80	182	69.9	12.0	178
	Sr	5.87	8.42	1.59	0.93	32.0	2.26	1.11	31.5
	V	0.152	0.074	0.016	0.043	0.370	0.150	0.056	0.310
	Zn	120.5	50.8	7.8	47.0	264	113	49.1	257

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.

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 level reported in the literature for normal and for goitrousthyroid vary widely (Table 5). This can be explained by a dependence of ChE on many factors, including the region of the thyroid, from which the sample was taken, age, gender, ethnicity, mass of the gland, and the NG stage. Not all these factors were strictly controlled in cited studies. Another and, in our opinion, leading cause of inter-observer variability can be attributed to the accuracy of the analytical techniques, sample preparation methods, and inability of taking uniform samples from the affected tissues. It was insufficient quality control of results in these studies. In many reported papers tissue samples were ashed or dried at high temperature for many hours. In other cases, thyroid samples were treated with solvents (distilled water, ethanol, formalin etc). There is evidence that by use of these sample preparation methods some quantities of certain ChE are lost as a result of this treatment That concern not only such volatile halogen as Br, but also other ChE investigated in the study [94-96].

Table 5: 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 and goitrous thyroid according to data from the literature in comparison with our results (mg/kg, dry mass basis)

Tissue	**El**	**Published data [Reference]**			**This work**
		Median of means (n)*	**Min of means M or M±SD, (n)****	**Max of means M or M±SD, (n)****	**M±SD**
Normal	Al	33.6 (12)	0.33 (-) [58]	420 (25) [59]	10.5±13.4
	B	0.151 (2)	0.084 (3) [60]	0.46 (3) [60]	0.476±0.434
	Ba	0.67 (7)	0.0084 (83) [61]	≤5.0 (16) [62]	1.12±1.15
	Br	18.1 (11)	5.12 (44) [63]	284±44 (14) [64]	16.3±11.6
	Ca	1600 (17)	840±240 (10) [65]	3800±320 (29) [65]	1663±999
	Cl	6800 (5)	804±80 (4) [66]	8000 (-) [67]	3400±1452
	Cu	6.0 (61)	0.16 (83) [61]	220±22 (10) [66]	3.93±1.43
	Fe	252 (21)	56 (120) [68]	3360 (25) [59]	223±95
	I	1888 (95)	159±8 (23) [69]	5772±2708 (50) [70]	1841±1027
	K	4300 (17)	46.4±4.8 (4) [66]	6090 (17) [62]	6418±2625
	Li	6.3 (2)	0.092 (-) [71]	12.6 (180) [72]	0.0208±0.0154
	Mg	390 (16)	3.5 (-) [58]	1520 (20) [73]	296±134
	Mn	1.62 (40)	0.076 (83) [61]	69.2±7.2 (4) [66]	1.28±0.56
	Na	8000 (9)	438 (-) [74]	10000±5000 (11) [75]	6928±1730
	P	2860 (10)	16 (7) [76]	7520 (60) [63]	4290±1578
	S	11000 (3)	4000 (-) [67]	11800 (44) [63]	8259±2002
	Si	16.0 (3)	0.97 (-) [58]	143±6 (40) [77]	50.8±46.9
	Sr	0.61 (9)	0.055 (83) [61]	46.8±4.8(4) [66]	3.81±2.93
	V	0.065 (6)	0.0124 (2) [78]	18±2 (4) [66]	0.102±0.039
	Zn	110 (56)	2.1(-) [58]	820±204 (14) [64]	94.8±39.7
Goiter	Al	3.84 (6)	2.45 (123) [79]	840 (25) [59]	27.1±24.7
	B	-	-	-	1.71±1.19
	Ba	4.92 (1)	4.92±4.56 (51) [80]	4.92±4.56 (51) [80]	1.43±1.75
	Br	480 (4)	9 (5) [81]	777 (1) [82]	36.3±31.3
	Ca	3168 (8)	600 (1) [81]	9200 (1) [81]	1422±834
	Cl	-	-	-	9117±3866
	Cu	10.0 (33)	0.84 (1) [72]	353 (101) [83]	8.51±7.15
	Fe	390 (5)	128±52 (13) [84]	4848±3056 (11) [64]	337±321
	I	770 (44)	52 (1) [85]	2800 (4) [86]	1310±1433
	K	3725 (4)	276 (75) [87]	6030±620 (-) [88]	6610±2233
	Li	-	-	-	0.0281±.0.0117
	Mg	834 (4)	588±388 (13) [84]	1616 (70) [73]	356±119
	Mn	2.64 (21)	0.352 (130) [89]	34.9 (101) [90]	1.77±1.13
	Na	3360 (1)	3360 (25) [59]	3360 (25) [59]	11782±4342
	P	8200 (1)	8200±280 (-) [88]	8200±280 (-) [88]	5181±1798
	S	10300 (1)	10300±340 (-) [88]	10300±340 (-) [88]	10961±2091
	Si	64 (1)	45 (122) [88]	114 (122) [88]	81.3±57.3
	Sr	1.45 (2)	1.26 (25) [59]	1.64 (51) [80]	5.87±8.42
	V	3.92 (1)	3.92±8.84 (51) [80]	3.92±8.84 (51) [80]	0.152±0.074
	Zn	146 (25)	22.4 (130) [89]	1236±560 (2) [91]	120.5±50.8

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

Table 6: Differences between mean values (M±SEM) 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) in normal and goitrous thyroid

Element	Thyroid tissue				Ratio
	Norm n=105	Goiter n=46	Student's t-test *p*≤	U-test *p*	Goiter to Norm
Al	10.5±1.8	27.1±5.3	**0.0057**	**≤0.01**	2.58
B	0.476±0.058	1.71±0.26	**0.00013**	**≤0.01**	3.59
Ba	1.12±0.15	1.43±0.37	0.446	>0.05	1.28
Br	14.9±1.2	36.3±6.99	**0.0067**	**≤0.01**	2.44
Ca	1682±106	1422±164	0.188	>0.05	0.84
Cl	3400±174	9117±1223	**0.0011**	**≤0.01**	2.68
Cu	4.08±0.14	8.51±1.60	**0.012**	**≤0.01**	2.09
Fe	223±10	337±51	**0.034**	**≤0.01**	1.51
I	1841±107	1310±221	**0.035**	**≤0.01**	0.71
K	6418±290	6610±430	0.713	>0.05	1.03
Li	0.0208±0.0022	0.0281±0.0030	**0.037**	**≤0.01**	1.35
Mg	296±16	356±23	**0.037**	**≤0.01**	1,20
Mn	1.28±0.07	1.77±0.23	**0.048**	**≤0.01**	1.38
Na	6928±175	11782±836	**0.0000041**	**≤0.01**	1.70
P	4290±207	5181±383	**0.049**	**≤0.05**	1.21
S	8259±263	10961±446	**0.0000074**	**≤0.01**	1.33
Si	50.8±6.2	81.3±12.5	**0.037**	**≤0.01**	1.60
Sr	3.81±0.34	5.87±1.59	0.216	>0.05	1.54
V	0.102±0.005	0.152±0.016	**0.0072**	**≤0.01**	1.49
Zn	94.8±4.2	120.5±7.8	**0.0053**	**≤0.01**	1.27

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

Effect of goitroustransformationon ChE contents

From Table 6, it is observed that in goitrous tissue the mass fraction of Al, B, Br, Cl, and Cu are approximately 2.6, 3.6, 2.4, 2.7, and 2.1 times, respectively, higher and also mass fractions of Fe, Li, Mg, Mn, Na, P, S, Si, V, and Zn are almost in 51%,, 35%, 20%, 38%, 70%, 21%, 33%, 60%, 49%, and 27% respectively, higher than in normal tissues of the thyroid. In contrast, the mass fraction of I is 29% significantly lower. Thus, if we accept the ChE contents in thyroid glands in the control group as a norm, we have to conclude that with a goitrous transformation the levels of Al, B, Br, Cl, Cu, Fe, Li, Mg, Mn, Na, P, S, Si, V, and Zn in thyroid tissue significantly increased, whereas the level of I some decreased.

Role of ChE in goitroustransformation of the thyroid

Characteristically, elevated or reduced levels of ChE observed in goitrous tissues are discussed in terms of their potential role in the initiation and promotion of thyroid goiter. In other words, using the low or high levels of the ChE in goitroustissues researchers try to determine the goitrogenic role of the deficiency or excess of each ChE in investigated organ. In our opinion, abnormal levels of many ChE in NG could be and cause, and also effect of goitrous transformation. From the results of such kind studies, it is not always possible to decide whether the measured decrease or increase in ChE level in pathologically altered tissue is the reason for alterations or vice versa**.**

Aluminum

The trace element Al is not described as essential, because no biochemical function has been directly connected to it. At this stage of our knowledge, there is no doubt that Al overload impacts negatively on human health, including the thyroid function [97].

Boron

Trace element B is known to influence the activity of many enzymes [98]. Numerous studies have demonstrated beneficial effects of B on human health, including anti-inflammatorystimulus - reduces levels of inflammatory biomarkers, such as high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor α (TNF-α); as well as raises levels of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase [99]. Why B content in goitrousthyroid is higher than normal level and how an excess of B acts on thyroid are still to be cleared.

Bromine

This is one of the most abundant and ubiquitous of the recognized trace elements in the biosphere. Inorganic bromide is the ionic form of Br which exerts therapeutic as well as toxic effects. An enhanced intake of bromide could interfere with the metabolism of I at the whole-body level. In the thyroid gland the biological behavior of bromide is more similar to the biological behavior of iodide [100].

In our previous studies, we found a significant age-related increase of Br content in human thyroid [27,28,31-34]. Therefore, a goitrogenic and, probably, carcinogenic effect of excessive Br levels in the thyroid of old females was assumed. On the one hand, elevated levels of Br in NG tissues, observed in the present study, supports this conclusion. But, on the other hand, bromide compounds, especially potassium bromide (KBr), sodium bromide (NaBr), and ammonium bromide (NH_4Br), are frequently used as sedatives in Russia [101]. It may be the reason for elevated levels of Br in specimens of patients with NG.

Chlorine

Cl is a ubiquitous, extracellular electrolyte essential to more than one metabolic pathway. Cl exists in the ionic form (chloride) in the human body. In the body, it is mostly present as sodium chloride. Therefore, as usual, there is a correlation between Na and Cl contents in tissues and fluids of human body. It is well known that Cl mass fractions in samples depend mainly on the extracellular water volume, including the blood volumes, in tissues [102]. NG tissues are predominantly highly vascularized lesions [103]. Thus, it is possible to speculate that thyroid goiters are characterized by an increase of the mean value of the Cl mass fraction because the level of goiter vascularization is higher than that in normal thyroid tissue.

Coper

Cu is a ubiquitous element in the human body which plays many roles at different levels. Various Cu-enzymes (such as amine oxidase, ceruloplasmin, cytochrome-c oxidase, dopamine-monooxygenase, extracellular superoxide dismutase, lysyl oxidase, peptidylglycineamidatingmonoxygenase, Cu/Zn superoxide dismutase, and tyrosinase) mediate the effects of Cu deficiency or excess. Cu excess can have severe negative impacts. Cu generates oxygen radicals and many investigators have hypothesized that excess copper might cause cellular injury via an oxidative pathway, giving rise to enhanced lipid peroxidation, thiol oxidation, and, ultimately, DNA damage [104]. Thus, Cu accumulation in thyroid parenchyma with age may be involved in oxidative stress, dwindling gland function, and increasing risk of goiter or cancer [25,26,31,33,34]. The significantly elevated level of Cu in goitrousthyroid, observed in the present study, supports this speculation. However, an overall comprehension of Cu homeostasis and physiology, which is not yet acquired, is mandatory to establish Cu exact role in the thyroid goiter etiology and metabolism.

Iron.

It is well knownthat Fe as a trace element is involved in many very important functions and biochemical reactions of human body. Fe metabolism is therefore very carefully regulated at both a systemic and cellular level [105]. Under the impact of age and multiple environmental factors the Fe metabolism may become dysregulated with attendant accumulation of this metal excess in tissues and organs, including thyroid [25,26,29-34]. Most experimental and epidemiological data support the hypothesis that Fe overload is a risk factor for benign and malignant tumors [106]. This goitrogenic and oncogenic effect could be explained by an overproduction of ROS and free radicals [107].

Iodine

Compared to other soft tissues, the human thyroid gland has higher levels of I, because this element plays an important role in its normal functions, through the production of thyroid hormones (thyroxin and triiodothyronine) which are essential for cellular oxidation, growth, reproduction, and the activity of the central and autonomic nervous system. Goitrous transformation is accompanied by a partial loss of tissue-specific functional features, which leads to a significant reduction in I content associated with functional characteristics of the human thyroid tissue.

Lithium

The results of lifelong Li-poor nutrition of animals show that Li is essential to the fauna, and thus, to humans as well [108]. Li-poor nutrition has a negative influence on some enzyme activity, mainly the enzymes of the citrate cycle, glycolysis, and of nitrogen metabolism [108]. On the other hand, Li is widely used in medicine as a mood-stabilizing drug. Because of the active transport of Na^+/I^- ions, Li is accumulated in the thyroid gland at a concentration 3 - 4 times higher than that in the plasma. It can inhibit the formation of colloid in thyrocytes, change the structure of thyroglobulin, weaken the iodination of tyrosines, and disrupt their coupling [109]. In addition, it reduces the clearance of free thyroxine in the serum, thereby indirectly reducing the activity of 5-deiodinase type 1 and 2 and reducing the deiodination of these hormones in the liver [109]. All these actions may cause the development of goiter.

Magnesium

Mg is abundant in the human body. This element is essential for the functions of more than 300 enzymes (e.g. alkaline phosphatases, ATP-ases, phosphokinases, the oxidative phosphorylation pathway). It plays a crucial role in many cell functions such as energy metabolism, protein and DNA syntheses, and cytoskeleton activation. Moreover,Mg is involved in the thyroid function and plays a central role in determining the clinical picture associated with thyroid disease [110]. The higher Mg levels in NG than do normal tissues, possibly is a result of the high Mg requirement of growing cells.

Manganese

Trace element Mn is a cofactor for numerous enzymes, playing many functional roles in living organisms. The Mn-containing enzyme, manganese superoxide dismutase (Mn-SOD), is the principal antioxidant enzyme which neutralizes the toxic effects of reactive oxygen species. It has been speculated that Mn interferes with thyroid hormone binding, transport, and activity at the tissue level [111]. However, an overall comprehension of Mn homeostasis and physiology, which is not yet acquired, is mandatory to establish Mn exact role in the thyroid goiter etiology and metabolism.

Sodium

Knowledge concerning ion regulation in many normal and abnormal cell processes has had a rapid development. It was found, among other regulations, that sodium-calcium exchange is associated with the cytoskeleton and the cell membrane. A hypothesis was eventually established that a wide variety of pathological phenomena ranging from acute cell death to chronic processes, such as neoplasia, all have a common series of cellular reactions [112]. Furthermore, iodide (I^-), an essential constituent of the thyroid hormones, is actively transported into the thyroid via the Na^+/I^- symporter (NIS), a key plasma membrane glycoprotein [113]. In addition, Na is mainly an extracellular electrolyte and its elevated level in NG might link with a higher goiter vascularization in comparison with the normal thyroid (see *Chlorine*).

Phosphorus

P is necessary for several, various biological roles in the signal transduction of cells and energy exchange of human body. About 80%–90% of P is founded in teeth and bones in the form of hydroxyapatite. Thyroid hormones play an important role in homeostasis of Ca and P levels by their direct action on bone turnover and, as a consequence, Ca and P metabolism is frequently disturbed in thyroid dysfunction with a significant increase in the P serum levels [114]. The elevated level of P in serum results the higher content of this element in NG tissue, because the goiter vascularization is higher in comparison with the normal thyroid. Besides, the elevated level of thyroid phospholipids in NG is common [115].

Sulfur

Proteins contain between 3 and 6% of sulfur amino acids. Sulfur amino acids contribute substantially to the maintenance and integrity of the cellular systems by influencing the cellular redox state and the capacity to detoxify toxic compounds, free radicals and reactive oxygen species (ROS) [116]. ROS are generated during normal cellular activity and may exist in excess in some pathophysiological conditions, such as inflammation. Therefore exploring fundamental aspects of sulfur metabolism such as the antioxidant effects of sulfur-containing amino acids [117] may help elucidate the mechanism by which the S content increases in NG. Thus, it might be assumed that the elevated S level in goitrous thyroid reflects an increase in concentration of ROS in goiter tissue.

Silicon

Si as a trace element is essential to some specific biological functions in humans [118]. For example, Si is necessary for the association between cells and one or more macromolecules such as osteonectin, which affects cartilage composition and ultimately cartilage calcification [119].However, an association between the disorders of thyroid function and the Si excess in the diets was found [120]. An increase in the thyrotropin (TSH) level in rats was observed after Si-treatment, without statistically significant differences in thyroid hormones concentrations between the test and control groups of animals [121].

Vanadium

V complexes are cofactors for several enzymes that maintaining hemostasis in health and pathology. For example, V compounds normalized blood pressure, ischemia and the metabolism of the thyroid [122]. However, all V compounds have been considered toxic and a goitrogenic and carcinogenic role of V on the thyroid was proposed [123]. V compounds promotes the induction and perpetuation of an inflammatory reaction in the thyroid [123]. Thus, the elevated V level in thyroid may be a cause of the gland disfunctions, NG and cancer.

Zinc

Zn is active in more than 300 proteins and over 100 DNA-binding proteins, including the tumor suppressor protein p53, a Zn-binding transcription factor acting as a key regulator of cell growth and survival upon various forms of cellular stress. p53 is mutated in half of human tumors and its activity is tightly regulated by metals and redox mechanisms. On the other hand, excessive intracellular Zn concentrations may be harmful to normal metabolism of cells [124]. By now much data has been obtained related both to the direct and indirect action of intracellular Zn on the DNA polymeric organisation, replication and lesions, and to its vital role for cell division [125,126]. Other actions of Zn have been also described. They include its action as a potent anti-apoptotic agent [127-131]. All these facts allowed us to speculate that age-related overloadZn content in female thyroid, as was found in our previous study [25,29,31,33], is probably one of the factors in etiology of thyroid goiter and malignant tumors. Therefore, the elevated Zn level in NG in comparison with normal level, detected in this study, supports our hypothesis.

Our findings show that mass fraction of Al, B, Br, Cl, Cu, Fe, I, Li, Mg, Mn, Na, P, S, Si, V, and Zn are significantly different in NG as compared to normal thyroid tissues (Tables 6). Thus, it is plausible to assume that levels of these ChE in thyroid tissue can be used as NG markers. However, this subjects needs in additional studies.

Limitations

This study has several limitations. Firstly, analytical techniques employed in this study measure only twenty ChE (Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn) mass fractions. Future studies should be directed toward using other analytical methods which will extend the list of ChEinvestigated in normal and goitrous thyroid. Secondly, the sample size of NG group was relatively small. It was not allow us to carry out the investigations of ChE contents in NG group using differentials like gender, histological types of goiter, stage of disease, and dietary habits of healthy persons and patients with NG. Lastly, generalization of our results may be limited to Russian population. Despite these limitations, this study provides evidence on goiter-specific tissue Al, B, Br, Cl, Cu, Fe, I, Li, Mg, Mn, Na, P, S, Si, V, and Zn level alteration and shows the necessity to continue ChE research of goitrous thyroid.

CONCLUSION

In this work, ChE measurements were carried out in the tissue samples of normal thyroid and colloid NG using two instrumental analytical methods: non-destructive neutron activation analysis with high resolution spectrometry of short-lived radionuclides and inductively coupled plasma atomic emission spectrometry. It was shown that the combination of these methods is an adequate analytical tool for the estimation of twentyChE(Al, B, Ba, Br, Ca, Cl, Cu, Fe, I, K, Li, Mg, Mn, Na, P, S, Si, Sr, V, and Zn) contents in the tissue samples of intact and affected human thyroid, including needle-biopsy cores. It was observed that in goitrous tissues content of Al, B, Br, Cl, Cu, Fe, Li, Mg, Mn, Na, P, S, Si, V, and Zn significantly increased whereas the level of I decrease in a comparison with the normal thyroid tissues. In our opinion, the data of presented study strongly imply that ChE play a significant role in thyroid health and the etiology of colloid NG. It was supposed that the found differences in levels of ChEin affected thyroid tissue can be used as colloid NG markers.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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