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Determination the Content of Bromine, Calcium, Chlorine, Iodine, Potassium, Magnesium, Manganese, and Sodium in the Nodular Goiter of Human Thyroid Gland using Neutron Activation Analysis

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Abstract

Nodular goiter (NG) is a big medical and social problem. The aim of this exploratory study was to examine the content of bromine (Br), calcium (Ca), chlorine (Cl), iodine (I), potassium (K), magnesium (Mg), manganese (Mn), and sodium (Na) in the normal thyroid and in the thyroid tissues with diagnosed colloid NG. Thyroid contents of eight chemical elements (ChE) were determined in 46 subjects with colloid NG and 105 healthy populations. Measurements were done by non-destructive instrumental activation analysis using neutrons of nuclear reactor and high-resolution spectrometry of gamma-radiation of short-lived radionuclides. Investigated samples were divided into two parts. One was used for morphological examination while the other was for ChE analysis. A decrease in level of I, as well as the increase in contents of Br, Cl, Mg, and Na in goitrous tissue was found. The study showed that the goutrous transformation was accompanied by considerable changes in ChE contents of thyroid parenchyma.

Keywords: colloid nodular goiters; intact thyroid; chemical elements; instrumental neutron activation analysis

Introduction:

No less than 10 % of the world population is affected by thyroidal goiter detected during the examination and palpation and most of these pathological changes are nodular goiters (NG) [1]. But, using ultrasonography NG can be found in almost 70% of the general population [2]. NG is benign disease; nevertheless, during clinical examination, it can mimic malignant tumors [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 found that I excess has severe effects on human health and associated with the presence of thyroidal dysfunctions 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].

In addition to I, many other ChE are involved in essential physiological functions [13]. Essential or toxic (goitrogenic, mutagenic, carcinogenic) properties of ChE depend on tissue-specific need or tolerance, respectively [13]. Deficiency, overload or an imbalance of the ChE may result in cellular dysfunction, 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 employed for the investigation of I and other ChE levels in the normal and pathological thyroid gland [16-22]. Level of I in the normal gland was studied in relation to age, gender and some non-thyroidal diseases [23,24].

After that, variations of many other ChE content with age in the thyroid of males and females were investigated and age- and gender-dependence of some ChE was observed [25-41]. Furthermore, a significant difference between some ChE mass fractions in normal and malignant thyroid was demonstrated [42-47]. For example, a strongly pronounced tendency of age-related increase in bromine (Br), calcium (Ca), and I mass fractions was demonstrated by using non-destructive instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR) [27,28]. In addition, a significant positive correlation was seen between the contents of I and sodium (Na) in female thyroid, and also between I and Ca in male thyroid [27,28]. It was concluded that high intra-thyroidal I and Ca concentrations are probably one of the main factors acting in both initiation and promotion stages of thyroid goitrogenesis and carcinogenesis [27,28] as it was earlier shown by us for Ca and some other chemical elements in prostate gland [48-51]. Moreover, it seems fair to suppose that besides I and Ca, such ChE as Br, chlorine (Cl), potassium (K), magnesium (Mg), manganese (Mn), and Na also play a role in the pathophysiology of the thyroid.

The research objective of this work was to evaluate the Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions in NG tissue using non-destructive instrumental neutron activation analysis with high resolution spectrometry of gamma-radiations from activated short-lived radionuclides (INAA-SLR) and also to compare the contents of these ChE in the goitrous thyroid with those in intact (normal) gland of apparently healthy persons.

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

Material and Methods:

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 MRRC 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. 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.

All tissue samples were divided into two parts using a titanium scalpel [52]. One was used for morphological study while the other was for ChE analysis. After the samples intended for ChE analysis were weighed, they were freeze-dried and homogenized [53].

Details of sample preparation, activation by neutrons of nuclear reactor, gamma-spectrometry, and quality insurance using certified reference material (CRM) of International Atomic Energy Agency IAEA H-4 (animal muscle) were presented in our earlier publications concerning the INAA-SLR of ChE contents in human thyroid, scalp hair, and prostate [19,54-57].

A dedicated computer program for INAA-SLR mode optimization was used [58]. All tissue samples were prepared in duplicate, and mean values of ChE contents were used in final calculation. 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 goitrous thyroid) was evaluated by the parametric Student's *t*-test and non-parametric Wilcoxon-Mann-Whitney *U*-test.

Results:

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

The comparison of our results with published data for Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction in normal and goitrous thyroid [59-81] is shown in Table 2.

The ratios of means and the difference between mean values of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions in normal and goitrous thyroid are presented in Table 3.

Tissue/Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Normal								
Br	16.3	11.6	1.3	1.90	66.9	13.6	2.57	51.0
Ca	1692	1022	109	414	6230	1451	460	3805
Cl	3400	1452	174	1030	6000	3470	1244	5869
I	1841	1027	107	114	5061	1695	230	4232
K	6071	2773	306	1740	14300	5477	2541	13285
Mg	285	139	16.5	66.0	930	271	81.6	541
Mn	1.35	0.58	0.07	0.510	4.18	1.32	0.537	2.23
Na	6702	1764	178	3050	13453	6690	3855	10709
Goiter								
Br	36.3	31.3	7.0	8.00	131	26.6	8.95	110
Ca	1393	855	168	209	4333	1280	258	3219
Cl	9117	3866	1223	4226	16786	8259	4504	15869
I	1141	931	145	29	3715	927	106	3617

K	6518	2304	443	3353	12222	6185	3395	10984
Mg	351	148	28	13	612	371	45.5	550
Mn	1.78	1.13	0.23	0.370	5.50	1.70	0.418	4.12
Na	11335	3597	705	7229	22381	10413	7277	19009

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 Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in normal (n=105) and goitrous (n=46) thyroid

Tissue / Element	Published data [Reference]			This work
	Median of means (n)*	Minimum of means M or M±SD, (n)**	Maximum of means M or M±SD, (n)**	M±SD
Normal				
Br	18.1 (11)	5.12 (44) [59]	284±44 (14) [60]	16.3±11.6
Ca	1600 (17)	840±240 (10) [61]	3800±320 (29) [61]	1692±1022
Cl	6800 (5)	804±80 (4) [62]	8000 (-) [63]	3400±1452
I	1888 (95)	159±8 (23) [64]	5772±2708 (50) [65]	1841±1027
K	4400 (16)	46.4±4.8 (4) [62]	6090 (17) [66]	6071±2773
Mg	390 (16)	3.5 (-) [67]	1520 (20) [68]	285±139
Mn	1.62 (40)	0.076 (83) [69]	69.2±7.2 (4) [62]	1.35±0.58
Na	8000 (9)	438 (-) [70]	10000±5000 (11) [71]	6702±1764
Goiter				
Br	480 (5)	9 (5) [72]	777 (1) [73]	36.3±31.3
Ca	3168(8)	600 (1) [72]	9200 (1) [72]	1393±855
Cl	-	-	-	9117±3866
I	770 (44)	52 (1) [74]	2800 (4) [75]	1141±931
K	3725 (4)	276 (75) [76]	6030±620 (-) [77]	6518±2304
Mg	834 (4)	588±388 (13) [78]	1616 (70) [68]	351±148
Mn	2.64 (21)	0.352 (130) [79]	34.9 (101) [80]	1.78±1.13
Na	3360 (1)	3360 (25) [81]	3360 (25) [81]	11335±3597

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

Table 2. Median, minimum and maximum value of means Br, Ca, Cl, I, K, Mg, Mn, and Na contents in normal and goitrous thyroid according to data from the literature in comparison with our results (mg/kg, dry mass basis)

Element	Thyroid tissue				Ratio
	Normal thyroid n=105	Thyroid goiter n=46	Student's t-test *p*≤	U-test *p*	Goiter to Norm
Br	16.3±1.3	36.3±7.0	**0.0106**	**≤0.01**	2.23
Ca	1692±109	1393±168	0.118	>0.05	0.82
Cl	3400±174	9117±1223	**0.0011**	**≤0.01**	2.68
I	1841±107	1141±145	**0.0002**	**≤0.01**	0.62
K	6071±306	6518±443	0.410	>0.05	1.07
Mg	285±17	351±28	**0.0491**	**≤0.05**	1.23
Mn	1.35±0.07	1.78±0.23	0.079	>0.05	1.32
Na	6702±1785	11335±705	**0.00000066**	**≤0.01**	1.69

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

Table 3. Differences between mean values (M±SEM) of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in normal and goitrous thyroid

Discussion:

Precision and accuracy of results:

Previously found good agreement of the Br, Ca, Cl, I, K, Mg, Mn, and Na contents analyzed by INAA-SLR with the certified data of CRM IAEA H-4 [19,54-57].indicates an acceptable accuracy of the results obtained in the present study of ChE of the thyroid samples presented in Tables 1–3.

The mean values and all selected statistical parameters were calculated for eight ChE (Br, Ca, Cl, I, K, Mg, Mn, and Na) mass fractions (Table 1). The mass fraction of Br, Ca, Cl, I, K, Mg, Mn, and Na were measured in all, or a major portion of normal and goitrous tissue samples.

Comparison with published data:

In general, values of means obtained in present study for Br, Ca, Cl, I, K, Mg, Mn, and Na contents in the normal human thyroid (Table 2) agree well with median of means reported by other researchers [59-81]. A number of values for ChE mass fractions were not expressed on a dry mass basis by the authors of the cited references. However, we calculated these values using published data for water (75%) [82] and ash (4.16% on dry mass basis) [83] contents in thyroid of adults.

Data cited in Table 2 for normal thyroid also includes samples obtained from patients who died from different non-endocrine diseases. In our previous study it was shown that some non-endocrine diseases can effect on ChE contents in thyroid [24]. Moreover, in many studies the "normal" thyroid means a visually non-affected tissue adjacent to benign or malignant thyroidal nodules. However, there are no data on a comparison between the ChE contents in such kind of samples and those in thyroid of healthy persons, which permits to confirm their identity.

In goitrous tissues (Table 2) our results were comparable with published data for Ca, I, K, Mg, and Mn contents. The obtained mean for Br was approximately one order of magnitude lower than the median of previously reported means, but within the range of means (Table 2). The obtained mean for Na was 3.4 times higher than the only reported result (Table 2). No published data referring Cl contents of goitrous thyroid tissue were found.

The range of means of levels of Br, Ca, Cl, I, K, Mg, Mn, and Na reported in the literature for normal and goitrous thyroid vary widely (Table 2). This can be explained by a dependence of ChE content on many factors, including "normality" of thyroid samples (see above), the region of the thyroid, from which the sample was taken, age, gender, ethnicity, mass of the gland, and the goiter stage. Not all these factors were strictly controlled in cited studies. However, in our opinion, the leading causes 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 scientific reports, 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 during ashing, drying and digestion at high temperature some quantities of certain ChE are lost as a result of this treatment. That concerns not only such volatile halogen as Br, but also other ChE investigated in the study [53,84,85].

Effect of goitrous transformation on ChE contents:

From Table 3, it is observed that in goitrous tissues the mass fractions of Ca and I are 18% and 38%, respectively, lower whereas mass fractions of Br, Cl, K, Mg, Mn, and Na are approximately 2.2, 2.7, 1.1, 1.2, 1.3, and 1.7 times, respectively, higher than in normal tissues of the thyroid. However, the changes for Br, Cl, I, Mg, and Na are only statistically significant. 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 Br, Cl, I, Mg, and Na contents in thyroid tissue significantly changed.

Role of ChE in goitrous transformation 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 goiter. In other words, using the low or high levels of the ChE found in goitrous tissues, 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.

Bromine:

This is one of the most abundant and ubiquitous of the recognized ChE in the biosphere. Inorganic bromide is the ionic form of bromine which exerts therapeutic as well as toxic effects. An enhanced intake of bromide could interfere with the metabolism of iodine at the whole-body level. In the thyroid gland the biological behavior of bromide is more similar to the biological behavior of iodide [86]. Moreover, many studies indicate that bromate (BrO^{3-}) and potassium bromate ($KBrO_3$) are carcinogens [87-89]. Bromate is formed as a drinking water ozone disinfection by-product and also used in some food and consumer product [88]. Potassium bromate is a chemical oxidizing agent that used extensively in food and cosmetic industries [88,89]. Potassium bromate is also found in drinking water as a disinfection by-product of surface water ozonation [87].

In our previous studies it was found a significant age-related increase of Br content in human thyroid [25-28]. This finding correlated with a significant age-related increase of thyroid cancer incidents. Furthermore, elevated levels of Br in cancerous thyroid and malignant tumor of prostate were indicated [42-50,90].

Thus, on the one hand, the accumulated data suggest that Br might be responsible for thyroid goiter development. But, on the other hand, Br compounds, especially potassium bromide (KBr), sodium bromide (NaBr), and ammonium bromide (NH_4Br), are frequently used as sedatives in Russia [91]. It may be the reason for elevated levels of Br in specimens of patients with NG. Anyway, the accumulation of Br in goitrous thyroids could possibly be explored for diagnosis of NG.

Chlorine:

Cl is a ubiquitous, extracellular electrolyte essential to more than one metabolic pathway. Cl exists in the form of 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 in tissues [92]. Goitrous tissues contain more colloid that normal thyroid. Because colloid is extracellular liquid, it is possible to speculate that colloid NG are characterized by an increase of the mean value of the Cl mass fraction because the relative content of colloid is higher than that in normal thyroid tissue. Overall, the elevated levels of Cl in goutrous thyroids could possibly be explored for diagnosis of NG.

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 probably accompanied by a partial loss of tissue-specific functional features, which leads to a modest reduction in I content associated with functional characteristics of the human thyroid tissue. Little reduced level of I content in goitrous thyroids could possibly be explored for diagnosis of NG.

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 plays a central role in determining the clinical picture associated with thyroid disease [93]. Little elevated Mg level in NG tissues possibly caused by the high Mg requirement of growing cells [94]. Thus, the modest elevated levels of Mg in goitrous thyroids could possibly be explored for diagnosis of NG.

Sodium:

Na is mainly an extracellular electrolyte and its elevated level in goitrous thyroid might link with a high content of colloid (see *Chlorine*). Anyway, it seems that the elevated levels of Na in goitrous thyroids could possibly be explored for diagnosis of NG.

Limitations:

This study has several limitations. Firstly, analytical techniques employed in this study measure only eight ChE (Br, Ca, Cl, I, K, Mg, Mn, and Na) mass fractions. Future studies should be directed toward using other analytical methods which will extend the list of ChE investigated in normal and goitrous thyroid tissue. Secondly, the sample size of NG group was relatively small and prevented investigations of ChE contents in NG group using differentials like gender, histological types of colloid 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 Br, Cl, I, Mg, and Na level alteration and shows the necessity to continue ChE research of thyroid goiter.

Conclusion:

In this work, ChE analyses were carried out in the tissue samples of normal and goitrous thyroid using INAA-SLR. It was shown that INAA-SLR is an adequate analytical tool for the non-destructive determination of Br, Ca, Cl, I, K, Mg, Mn, and Na contents in the tissue samples of human thyroid glands, including core needle biopsies. It was observed that in NG content of I was little lower ($p<0.0002$) and contents of Br ($p<0.0106$), Cl ($p<0.0011$), Mg ($p<0.049$), and Na ($p<0.00000066$) were significantly higher than in normal tissues. In our opinion, the abnormal decrease in level of I, as well as the increase in levels of Br, Cl, Mg, and Na in goitrous tissue might demonstrate an involvement of these elements in etiology and pathogenesis of NG. It was supposed that elevated levels of Br, Cl, Mg, and Na, as well as little reduced levels of I in thyroid tissues can be used as goiter markers.

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Conflict of Interest:

The author has not declared any conflict of interests.

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