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RESEARCH ARTICLE

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Trace Element Contents in Thyroid of Patients with Diagnosed Colloid Nodular Goiter Determined by Energy Dispersive X-Ray Fluorescent Analysis

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SUMMARY

Background: Nodular goiter (NG) is an internationally important health problem. The aim of this exploratory study was to examine the content of bromine (Br), cooper (Cu), iron (Fe), rubidium (Rb), strontium (Sr), and zinc (Zn) in the normal thyroid and in the thyroid tissues with diagnosed colloid NG.

Methods: Thyroid tissue levels of six trace elements (TE) were prospectively evaluated in 46 patients with thyroid colloid NG and 105 healthy inhabitants. Measurements were performed using 109Cd radionuclide-induced energy-dispersive X-ray fluorescent analysis Tissue samples were divided into two portions. One was used for morphological study while the other was intended for TE analysis.

Results: It was found that contents of Br and Cu were significantly higher (2.61 and 2.01 times, respectively) and content of Sr were significantly lower (47%) in goitrous thyroid than in normal thyroid.

Conclusions: There are considerable changes in TE contents in the goitrous transformed tissue of thyroid.

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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 uninodular goitre or multinodular goiter [3]. NG are benign lesions; however, during clinical examination, they can mimic malignant tumors. NG can be hyperfunctioning, hypofunctioning, and normal functioning. Euthyroid NG 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 deficiency. However, it was found that NG is a frequent disease even in those countries and regions where the population is never exposed to iodine shortage [4]. Moreover, it was shown that iodine 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 iodine 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 in human body after industrial revolution plays a significant role in etiology of thyroidal disorders [12].

Besides iodine involved in thyroid function, other trace elements (TE) 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 TE depend on tissue-specific need or tolerance, respectively [13]. Excessive accumulation or an imbalance of the TE 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 iodine and other TE contents in the normal and pathological thyroid [16-22]. Iodine level in the normal thyroid was investigated in relation to age, gender and some non-thyroidal diseases [23,24]. After that, variations of TE content with age in the thyroid of males and females were studied and age- and gender-dependence of some TE was observed [25-41]. Furthermore, a significant difference between some TE 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 some TE in the maintenance of thyroid growth and goitrogenesis. Having this in mind, our aim was to assess the bromine (Br), copper (Cu), iron (Fe), rubidium (Rb), strontium (Sr), and zinc (Zn) contents in NG tissue using energy dispersive X-ray fluorescent analysis (EDXRF). A further aim was to compare the levels of these TE in the goitrous thyroid with those in intact

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(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/or national research committee and with the 1964 Helsinki declaration and its later amendments, or with 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 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 TE 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 portions using a titanium scalpel [48]. One was used for morphological study while the other was intended for TE analysis. After the samples intended for TE analysis were weighed, they were freeze-dried and homogenized [49]. The pounded sample weighing about 8 mg was applied to the piece of Scotch tape serving as an adhesive fixing backing.

To determine the contents of the TE by comparison with known data for standard, aliquots of commercial, chemically pure compounds and synthetic reference materials were used [50]. The microliter standards were placed on disks made of thin, ash-free filter papers fixed on the Scotch tape pieces and dried in a vacuum. Ten subsamples of the Certified Reference Material (CRM) IAEA H-4 (animal muscle) weighing about 8 mg were analyzed to estimate the precision and accuracy of results. The CRM IAEA H-4 subsamples were prepared in the same way as the samples of dry homogenized thyroid tissue.

Details of the relevant facility for EDXRF, source with 109Cd radionuclide, methods of analysis and the results of quality control were presented in our earlier publications concerning the EDXRF analysis of human thyroid and prostate tissue [25,26,51].

All thyroid samples were prepared in duplicate, and mean values of TE contents were used in final calculation. Using Microsoft Office Excel software, 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 TE contents in normal and NG tissue. The difference in the results between two groups (normal thyroid 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 six TE in ten sub-samples of CRM IAEA H-4 (animal muscle) and the certified values of this material.

Table 2 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, Cu, Fe, Rb, Sr, Zn mass fraction in normal and goitrous thyroid.

The comparison of our results with published data for Br, Cu, Fe, Rb, Sr, and Zn mass fraction in normal and goitrous thyroid is shown in Table 3 [9,52-66].

The ratios of means and the difference between mean values of Br, Cu, Fe, Rb, Sr, Zn mass fractions in normal and goitrous thyroid are presented in Table 4.

Table 1: EDXRF data Br, Cu, Fe, Rb, Sr, and Zn contents in the IAEA H-4 (animal muscle) reference material compared to certified values (mg/kg, 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±1.2
Cu	4.0	3.6 - 4.3	C	3.9±1.1
Fe	49	47 - 51	C	48±9
Rb	18	17 - 20	C	22±4
Sr	0.1	-	N	<1
Zn	86	83 - 90	C	90±5

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

Table 2: Some statistical parameters of Br, Cu, Fe, Rb, Sr, 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 n=105	Br	13.9	12.0	1.3	1.4	54.4	10.0	2.23	50.8
	Cu	4.23	1.52	0.18	0.50	7.50	4.15	1.57	7.27
	Fe	222	102	11	47.1	512	204	65.7	458
	Rb	9.03	6.17	0.66	1.80	42.9	7.81	2.48	25.5
	Sr	4.55	3.22	0.37	0.10	13.7	3.70	0.48	12.3
	Zn	112	44.0	4.7	6.10	221	106	35.5	188
Goiter n=46	Br	36.3	31.3	7.0	8.0	131	26.6	8.95	110
	Cu	8.51	7.15	1.6	2.9	34.5	5.95	3.00	26.2
	Fe	287	242	38	54.9	1052	197	55.2	902
	Rb	7.70	3.86	0.60	1.0	16.6	6.85	1.23	15.8
	Sr	2.43	2.73	0.49	0.80	13.7	1.64	0.80	10.6
	Zn	112	50	7.8	22.0	235	103	47.0	215

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 3: Median, minimum and maximum value of means Br, Cu, Fe, Rb, Sr, and Zn contents in normal and goitrous thyroid according to data from the literature in comparison with our results (mg/kg, dry mass basis)

Tissue	Element	Published data [Reference]			This work
		Median of means (n)*	Minimum of means M or M±SD, (n)**	Maximum of means M or M±SD, (n)**	M±SD
Normal	Br	18.1 (11)	5.12 (44) [52]	284±44 (14) [53]	13.9±12.0
	Cu	5.94 (61)	0.16 (83) [54]	220±22 (10) [55]	4.23±1.52
	Fe	252 (21)	56 (120) [56]	2444±700 (14) [53]	222±102
	Rb	12.3 (9)	≤0.85 (29) [57]	294±191 (14) [53]	9.03±6.17
	Sr	0.73 (9)	0.55±0.26 (21) [58]	46.8±4.8 (4) [55]	4.55±3.22
	Zn	118 (55)	1.08 (120) [59]	820±204 (14) [53]	112±44
Goiter	Br	480 (4)	9 (5) [60]	777 (1) [61]	36.3±31.3
	Cu	6.52 (8)	1.04 (130) [9]	120±52 (11) [53]	8.51±7.15
	Fe	390 (5)	128±52 (13) [62]	4848±3056 (11) [53]	287±242
	Rb	7.5 (2)	7.0 (10) [63]	864±148 (11) [53]	7.70±3.86
	Sr	1.45 (2)	1.26 (25) [64]	1.64±1.44 (51) [65]	2.43±2.73
	Zn	153 (8)	22.4 (130) [9]	1236±560 (2) [66]	112±50

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

Table 4: Differences between mean values (M±SEM) of Br, Cu, Fe, Rb, Sr, and Zn mass fraction (mg/kg, dry mass basis) in normal and goitrous thyroid

Element	Thyroid tissue				Ratio
	Norm n=105	Goiter n=46	Student's t-test $p\leq$	U-test p	Goiter to Norm
Br	13.9±1.3	36.3±7.0	**0.005**	**≤0.01**	2.61
Cu	4.23±0.18	8.51±1.60	**0.015**	**≤0.01**	2.01
Fe	222±11	287±38	0.106	>0.05	1.29
Rb	9.03±0.66	7.70±0.60	0.137	>0.05	0.85
Sr	4.55±0.37	2.43±0.49	**0.001**	**≤0.01**	0.53
Zn	112±5	112±8	0.997	>0.05	1.00

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

Discussion

Precision and Accuracy of Results

Good agreement of the Br, Cu, Fe, Rb, Sr, and Zn contents analyzed by EDXRF with the certified data of CRM IAEA H-4 (Table 1) indicates an acceptable accuracy of the results obtained in the study of TE of the thyroid samples presented in Tables 2–4.

The mean values and all selected statistical parameters were calculated for six trace elements (Br, Cu, Fe, Rb, Sr, and Zn) mass fractions (Table 2). The mass fraction of Br, Cu, Fe, Rb, Sr, and Zn were measured in all, or a major portion of normal and goitrous tissue samples.

Comparison with Published Data

In a general sense values obtained for Br, Cu, Fe, Rb, Sr, and Zn contents in the normal and goitrous thyroid (Table 3) agree well with median of mean values reported by other researches [9,52-66]. A number of values for TE 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%) and ash (4.16% on dry mass basis) contents in thyroid of adults [67,68].

Data cited in Table 3 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 TE 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 TE contents in such kind of samples and those in thyroid of healthy persons, which permits to confirm their identity.

In goitrous tissues (Table 3) our results were comparable with published data for Cu, Fe, Rb, Sr, and Zn contents. The obtained mean for Br was one order of magnitude lower median of previously reported means but inside the range of means (Table 3).

The range of means of Br, Cu, Fe, Rb, Sr, and Zn level reported in the literature for normal and goitrous thyroid vary widely (Table 3). This can be explained by a dependence of TE 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 TE are lost as a result of this treatment. That concerns not only such volatile halogen as Br, but also other TE investigated in the study [69-71].

Effect of Goitrous Transformation on TE Contents

From Table 4, it is observed that in goitrous tissue the mass fraction of Sr is 47% lower whereas mass fractions of Br and Cu are 2.61 and 2.01 times, respectively, higher than in normal tissues of the thyroid. Thus, if we accept the TE contents in thyroid glands in the control group as a norm, we have to conclude that with a goitrous transformation the Br, Cu, and Sr in thyroid tissue significantly changed.

Role of Trace Elements in Goitrous Transformation of the Thyroid

Characteristically, elevated or reduced levels of TE 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 TE in goitrous tissues researchers try to determine the goitrogenic role of the deficiency or excess of each TE in investigated organ. In our opinion, abnormal levels of many TE in goiter 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 TE 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 [72]. Moreover, many studies indicate that bromate ($BrO3-$) and potassium bromate ($KBrO3$) are carcinogens [73-75]. Bromate is formed as a drinking water ozone disinfection by-product and also used in some food and consumer product [73]. Potassium bromate is a chemical oxidizing agent that used extensively in food and cosmetic industries [74,75]. Potassium bromate is also found in drinking water as a disinfection by-product of surface water ozonation [73].

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 [42-47,76-79].

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 ($NH4Br$), are frequently used as sedatives in Russia [80]. 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.

Copper: This 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, peptidylglycineamidating monoxygenase, 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 [81-83]. 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]. The significantly elevated level of Cu in thyroid goitrous tissue, 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. Anyway, the accumulation of Cu in goitrous thyroids could possibly be explored for diagnosis of NG.

Representative literature data on the Cu content in NG are limited. Moreover, there are great contradictions in the results between the reported studies. For example, Kolomiitseva and Fal'fushins'ka at al. reported that the content of Cu was 1.3 and 2 times, respectively, higher in goitrous tissues compared with that in normal thyroid [84,85]. These data are in good agreement with our results. The completely opposite results were demonstrated by Błazewicz et al and Stojsavljević et al [9, 86]. They found that the content of Cu was reduced in NG.

Strontium: Obtained results for Sr content in NG agree well with data reported in old studies [64,65]. The role of Sr in the thyroid function and goitrogenesis is unknown. We can't explain why the Sr level in goitrous tissues is almost twice lower than in normal thyroid. Interestingly remark, however, that very similar result of reduced Sr content was indicated in thyroid adenoma [55]. Anyway, the significantly reduced level of Sr 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 six TE (Br, Cu, Fe, Rb, Sr, and Zn) mass fractions. Future studies should be directed toward using other analytical methods which will extend the list of chemical elements investigated in normal and goitrous thyroid. Secondly, the sample size of NG group was relatively small and prevented investigations of TE 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, Cu, and Sr level alteration and shows the necessity to continue TE research of thyroid goiter.

Conclusion

In this work, TE analysis was carried out in the tissue samples of normal and goitrous thyroid using EDXRF. It was shown that EDXRF is an adequate analytical tool for the non-destructive determination of Br, Cu, Fe, Rb, Sr, and Zn content in the tissue samples of human thyroid in norm and pathology, including needle-biopsy cores. It was observed that in goitrous tissues content of Sr was significantly lower, while contents of Br and Cu were significantly higher than in normal tissues. In our opinion, the abnormal decrease in level of Sr, as well as the increase in levels of Br, and Cu in goitrous tissue might demonstrate an involvement of these TE in etiology and pathogenesis of NG. It was supposed that elevated levels of Br and Cu, as well as reduced level of Sr in thyroid tissue can be used as goiter markers.

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Conflict of Interests

The author declares that there no conflict of interest.

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