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Evaluation of trace elements in riedel's struma using energy dispersive x-ray fluorescence analysis

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Abstract
Aim: Role of trace elements (TE) in etiology and pathogenesis of Riedel's disease (RD) is unclear. The aim of this exploratory study was to assess whether there were significant changes in thyroid tissue levels of five TE (Br, Fe Rb, Sr, and Zn) are present in the fibrotic transformed thyroid.
Methods: Five TE of thyroid tissue were determined in 6 patients with RD and 105 healthy populations. The measurements were performed using energy-dispersive X-ray fluorescent analysis.
Results: Elevated mean values of Br and Rb content were found in thyroid with RD in comparison with normal level (in 6.4 and 1.8 times, respectively).
Conclusions: There are considerable changes in some TE contents in tissue of thyroid with RD. Thus, it is reasonable to assume that the levels of these TE in thyroid tissue can be used as RD markers. However, this topic needs additional studies.

Keywords: riedel's disease, intact thyroid, trace elements, energy-dispersive X-ray fluorescent analysis

Introduction

Riedel's struma, also called Riedel's disease and Riedel's thyroiditis. is a peculiarly hard, infiltrative lesion (nodule) of the thyroid gland [1]. Riedel's disease (RD) is a rare form of chronic thyroiditis of unknown etiology associated with global or partial fibrosis of the thyroid gland, destruction of the thyroid follicle architecture, obliterative phlebitis, and a mixed infiltrate of lymphocytes, eosinophils, and plasma cells [1, 2]. Clinical differentiation between RD, Hashimoto's disease, and other thyroid benign and malignant nodules is often difficult [2, 3]. We hypothesized that disbalance of trace elements (TE) contents in thyroid tissue may play a significant role in etiology and pathogenesis of RD. Furthermore, specific levels of TE contents in fibrotic transformed thyroid tissue may be used as RD biomarkers.

For over 20th century, there was the dominant opinion that all thyroid nodules (TN), including RD, are the elementary consequence of iodine (I) deficiency. However, TN have been found to be a frequent disease even in those countries and regions where the population is never exposed to I deficiency [4]. Moreover, it was shown that iodine excess has severe effects on human health and associated with the development of thyroidal disfunctions and autoimmunity, nodular 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 TN 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]. In addition to I, many other TE are involved in essential physiological functions [13]. Essential or toxic (goitrogenic, mutagenic, carcinogenic) properties of TE depend on tissue-specific need or tolerance, respectively [13]. Deficiency, overload or an imbalance of the TE 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 TE 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 TE content with age in the thyroid of males and females were investigated and age- and gender-dependence of some TE was observed [25-41]. Furthermore, a significant difference between some TE mass fractions in normal and malignant thyroid was demonstrated [42-47].

So far, the etiology and pathogenesis of RD has to be considered as multifactorial. The present study was performed to clarify the role of some TE in the RD etiology. With this in mind, our aim was to assess the bromine (Br), iron (Fe), rubidium (Rb), strontium (Sr), and zinc (Zn) contents in normal thyroid tissue (NT) and RD tissue using non-destructive energy dispersive X-ray fluorescent analysis with ^{109}Cd radionuclide application for X-ray fluorescence excitation (^{109}Cd EDXRF). A further aim was to compare the levels of these TE in the NT and RD groups of samples.

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 with RD (n=6, 5 females and 1 male, mean age M±SD was 39±9 years, range 34-50) were hospitalized in the Head and Neck Department of the MRRC. Thick-needle puncture biopsy of suspicious lesion of the gland was performed for every persons, to allow morphological examination of affected thyroid tissue and to determine 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 RD.

Normal thyroid 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. Histological examination was used in the NT group to match the age criteria, as well as to confirm the absence of micro-nodules and underlying cancer. All thyroid samples were divided into two parts using a titanium scalpel [48]. One was used for morphological study while the other was for TE evaluation. All samples for TE analysis were weighed, freeze-dried and homogenized [49]. The pounded sample with mass 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]. Certified Reference Material of the International Atomic Energy Agency CRM IAEA H-4 (animal muscle) 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 thyroid tissue. Details of the relevant facility for ^{109}Cd EDXRF, source with ^{109}Cd radionuclide for X-ray fluorescence excitation, methods of analysis and the quality control of results were presented in our earlier publications concerning the ^{109}Cd 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 NT and RD groups of tissue samples. The difference in the results between two groups (NT and RD) was evaluated by the parametric Student's *t*-test and non-parametric Wilcoxon-Mann-Whitney *U*-test.

Results

Table 1 presents certain statistical parameters of the Br, Fe, Rb, Sr, Zn mass fraction in normal thyroid and Riedel's struma. Comparison of values obtained for Br, Fe, Rb, Sr, and Zn contents in the NT samples with median of means reported by other researches [52-58] depicts in Table 2.

The ratios of means and the difference between mean values of Br, Fe, Rb, Sr, Zn mass fractions in normal thyroid and Riedel's struma are presented in Table 3.

Table 1: Some statistical parameters of Br, Fe, Rb, Sr, and Zn mass fraction (mg/kg, dry mass basis) in normal thyroid and Riedel's struma

Tissue	Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Normal	Br	13.9	12.0	1.3	1.4	54.4	10.0	2.23	50.8
thyroid	Fe	222	102	11	47.1	512	204	65.7	458
n=105	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
Riedel's struma	Br	88.5	39.0	19.5	38.0	123	96.5	41	122
n=6	Fe	288	187	93	123	509	259	125	499
	Rb	16.1	4.8	2.4	9.4	20.3	17.4	9.90	20.2
	Sr	10.4	10.6	5.3	1.09	23.2	8.57	1.18	22.6
	Zn	78.5	28.8	14.4	58.0	121	67.5	58.5	117

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: Median, minimum and maximum value of means Br, Fe, Rb, Sr, and Zn contents in normal 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
thyroid	Fe	252 (21)	56 (120) [54]	2444±700 (14) [53]	222±102
	Rb	12.3 (9)	≤0.85 (29) [55]	294±191 (14) [53]	9.03±6.17
	Sr	0.61 (9)	0.055 (83) [56]	46.8±4.8 (4) [57]	4.55±3.22
	Zn	118 (55)	1.08 (120) [58]	820±204 (14) [53]	112±44

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

Table 3: Differences between mean values (M±SEM) of Br, Fe, Rb, Sr, and Zn mass fraction (mg/kg, dry mass basis) in normal thyroid and Riedel's struma

Element	Thyroid tissue				Ratio
	Normal thyroid n=105	Ridel's struma n=6	Student's t-test $p\leq$	U-test p	Ridel's struma to Normal thyroid
Br	13.9±1.3	88.5±19.5	**0.031**	**≤0.01**	6.37
Fe	222±11	288±93	0.533	>0.05	1.30
Rb	9.03±0.66	16.1±2.4	0.054	**≤0.05**	1.78
Sr	4.55±0.37	10.4±5.3	0.353	>0.05	2.29
Zn	112±5	78.5±14.4	0.095	>0.05	0.70

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

Discussion

As was shown before [25, 26, 51] good agreement of the Br, Fe, Rb, Sr, and Zn contents analyzed by EDXRF with the certified data of CRM IAEA H-4 indicates acceptable accuracy of the results obtained in the study of TE of the thyroid samples presented in Tables 1-3.

The mean values and all selected statistical parameters were calculated for five TE (Br, Fe, Rb, Sr, and Zn) mass fractions (Table 1). The mass fraction of Br, Fe, Rb, Sr, and Zn were measured in all, or a major portion of NT and RD tissue samples.

In a general sense values obtained for Br, Fe, Rb, Sr, and Zn contents in the NT samples (Table 2) agree well with median of mean values reported by other researches [52-58]. A number of values for TE mass fractions in literature were not expressed on a dry mass basis. However, we calculated these values using published data for water (75%) [59] and ash (4.16% on dry mass basis) [60] contents in thyroid of adults.

Data cited in Table 2 for NT 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.

The data on TE levels in RD tissue were not found in the literature.

The range of means of Br, Fe, Rb, Sr, and Zn level reported in the literature for NT tissue vary widely (Table 2). 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 its functional activity. Not all these factors were strictly controlled in cited studies. However, in our opinion, the main reason for the inter-observer discrepancy can be attributed to the accuracy of the analytical techniques, sample preparation methods, and the inability to take standardized samples from 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 [61, 62].

From Table 3, it is observed that in RD samples the mass fraction of Br and Rb are approximately 6.4 and 1.8 times, respectively, higher than in NT. Thus, if we accept the TE contents in the NT group as a norm, we have to conclude that with a fibrotic transformation the Br and Rb level in thyroid tissue significantly changed.

Characteristically, elevated or reduced levels of TE observed in affected tissues are discussed in terms of their potential role in the initiation and promotion of TN. In other words, using the low or high levels of the TE in TN researchers try to determine the role of the deficiency or excess of each TE in the TN etiology. In our opinion, abnormal levels of many TE in TN, including RD, could be and cause, and also effect of thyroid tissue 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. Nevertheless the differences between TE levels in normal and affected thyroid tissue could be used as RD markers.

This study has several limitations. Firstly, analytical techniques employed in this study measure only five TE (Br, Fe, Rb, Sr, and Zn) mass fractions. Future studies should be directed toward using other analytical methods which will extend the list of TE investigated in NT and RD. Secondly, the sample size of RD group was relatively small and prevented investigations of TE contents in RD group using differentials like gender, thyroid functional activity, stage of disease, dietary habits of healthy persons and patients with RD. Lastly, generalization of our results may be limited to Russian population. Despite these limitations, this study provides evidence on fibrotic-specific tissue Br and Rb level alteration and shows the necessity to continue TE research of RD.

Conclusion

In this work, TE measurements in tissue samples from NT and RD were performed using ^{109}Cd EDXRF. It was shown that ^{109}Cd EDXRF is an adequate analytical tool for the non-destructive determination of Br, Fe, Rb, Sr, and Zn content in tissue samples from healthy and affected human thyroid, including needle biopsy samples. It was observed that in RD contents of Br and Rb were significantly higher than in normal tissues. In our opinion, the presented study data strongly suggest that TE plays an important role in thyroid health, as well as in the etiology and pathogenesis of RD. It was assumed that the differences in TE levels in affected thyroid tissue could be used as RD markers.

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