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RESEARCH ARTICLE

THE POSSIBLE ROLE OF TRACE ELEMENTS IN THYROID HYPERTROPHIC AND ADENOMATOUS TRANSFORMATION

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Abstract

Background: Thyroid benign nodules (TBNs) are the most common diseases of this endocrine gland and are common worldwide. Among TBNs the colloid goiter (CG) and thyroid adenoma (TA) are very frequentdiseases. Evaluation of variant of TBNs is clinically important for subsequent therapeutic interventions, as well as for a clearer understanding the etiology of these disorders. The aim of this exploratory study was to examine differences in the content offifty trace elements (TE) in CG and TA tissues.
Methods: Thyroid tissue levels of TE have prospectively evaluated in 46 patients with CG and 19 patients with TA. Measurements have performed using a combination of non-destructive and destructive methods: instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides (INAA-LLR) and inductively coupled plasma mass spectrometry (ICPMS), respectively. Tissue samples were divided into two portions. One was used for morphological study while the other was intended for TE analysis.
Results: It was observed that in both CG and TA tissues the contents of Ag, Al, Cr, Hg, Mn, Th, and Zn increased, whereas the levels of Au, Be, Cs, Pb, Rb, Sb, Sc, Th, Yb, and Zr were unchanged in comparison with normal thyroid tissue. No differences were found between the TE contents of CG and TA.
Conclusions: From results obtained, it was possible to conclude that the common characteristics of CG and TA tissue samples were of a high level of Ag, Al, Cr, Hg, Mn, Th, and Zn in comparison with normal thyroid and, therefore, these TE could be involved in etiology and pathogenesis of thyroid disorders such as CG and TA.
Keywords: Inductively coupled plasma mass spectrometry, neutron activation analysis, thyroid nodules, trace elements.

INTRODUCTION

Thyroid benign nodules (TBNs) are universally encountered and frequently detected by palpation during a physical examination, or incidentally, during clinical imaging procedures. TBNs include non-neoplastic lesions, for example, colloid goiter (CG) and neoplastic lesion such as thyroid adenoma (TA)[1-3]. Evaluation of the variant of TBNs is clinically important for subsequent therapeutic interventions, which is why finding specific characteristics of CG and TA is necessary for the differential diagnosis of these thyroid disorders. For over 20th century, there was the dominant opinion that TBNs is the simple consequence of iodine deficiency. However, it was found that TBNs 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 TBNs[5-8]. It was also demonstrated that besides the iodine deficiency and excess many other dietary, environmental, and occupational factors are associated with the TBNsincidence[9-11]. Among these factors a disturbance of evolutionary stable input of many trace elements (TE) in human body after industrial revolution plays a significant role in etiology of TBNs[12].

Besides iodine, many other TE has also essential physiological functions[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 many 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]. A significant difference between some TE contents in CG and TA in comparison with normal thyroid was demonstrated[42-44]. To date, the etiology and pathogenesis of CG and TA must be considered as multifactorial. The present study was performed to find out differences in TE contents between the group of CG and TA samples, as well as to clarify the role of some TE in the etiology of thyroid lesions. Having this in mind, the aim of this exploratory study was to examine differences in the content of fifty TE in CG and TA tissues, using a combination of non-destructive instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides (INAA-LLR) and destructive inductively coupled plasma mass spectrometry (ICP-MS) method, and to compare the levels of these TEs in the cohort of CG and TA samples.

SUBJECTS AND METHODS

All patients suffered from CG (n=46, mean age M±SD was 48±12 years, range 30-64) and TA(n=19, mean age M±SD was 41±11 years, range 22-55) were hospitalized in the Head and Neck Department of the Medical Radiological Research Centre. All of them were inhabitants of environmentally sound (non-industrial and unpolluted) region. 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 (46 euthyroid CG, 4 toxic TA and 15 non-toxic TA). Histological conclusion for all thyroidal lesions was the CG (16 macro-follicular,13 micro-follicular, and 17 macro-micro-follicular) and TA (4 macro-follicular, 4 micro-follicular, 11 macro-micro follicular). All studies were approved by the Ethical Committees of the Medical Radiological Research Centre (MRRC), Obninsk (Reference number 115050610007, year 2017). 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 with comparable ethical standards

Titanium tools were used for biopsy, getting tissue samples from resected materials, and sample preparation to prevent contamination by many alloy metals from stainless steel[45]. All tissue samples were divided into two portions. 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[46]. Using INAA-LLR and ICP-MS, contents of fifty TE including silver (Ag), aluminum (Al), arsenic (As), gold (Au), boron (B),, beryllium (Be), bismuth (Bi), cadmium (Cd), cerium (Ce), cobalt (Co), chromium (Cr), cesium (Cs), dysprosium (Dy), iron (Fe), erbium (Er), europium (Eu), gallium (Ga), gadolinium (Gd), mercury (Hg), holmium (Ho), iridium (Ir), lanthanum (La), lithium (Li), lutecium (Lu), manganese (Mn), molybdenum (Mo), niobium (Nb), neodymium (Nd), nickel (Ni), lead (Pb), palladium (Pd), praseodymium (Pr), platinum (Pt), rubidium (Rb), antimony (Sb), scandium (Sc), selenium (Se), samarium (Sm), tin (Sn), terbium (Tb), tellurium (Te), thorium (Th), titanium (Ti), thallium (Tl), thulium (Tm), uranium (U), yttrium (Y), ytterbium (Yb), zinc (Zn), and zirconium (Zr) were detected in CG and TA tissue.

The pounded samples weighing about 10 mg (for biopsy) and 100 mg (for resected materials) were used for TE measurement by INAA-LLR. The content of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn were determined by INAA-LLR using a vertical channel of the Water-Water-Research nuclear reactor (Branch of Karpov Institute, Obninsk). After non-destructive INAA-LLR investigation the thyroid samples were used for ICP-MS. The samples were decomposed in autoclaves and aliquots of solutions were used to determine the Ag, Al, As, Au, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Dy, Er, Eu, Ga, Gd, Hg, Ho, Ir, La, Li, Lu, Mn, Mo, Nb, Nd, Ni, Pb, Pd, Pr, Pt, Rb, Sb, Se, Sm, Sn, Tb, Te, Th, Ti, Tl, Tm, U, Y, Yb, Zn, and Zr mass fractions by ICP-MS using an ICP-MS Thermo-Fisher "X-7" Spectrometer (Thermo Electron, USA).Information detailing with the NAA-LLR and ICP-MS methods used and other details of the analysis were presented in our earlier publications concerning TE contents in human thyroid[29,30,35], prostate[47-52], and scalp hair[53]. To determine contents of the TE by comparison with a known standard, biological synthetic standards (BSS) prepared from phenol-formaldehyde resins were used[54]. 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. A dedicated computer program for INAA-LLR mode optimization was used[55]. All thyroid samples were prepared in duplicate, and mean values of TE contents were used in final calculation. Mean values of TE contents were used in final calculation for the Ag, Co, Cr, Hg, Rb, Sb, Se, and Zn mass fractions measured by INAA-LLR and ICP-MS methods. Using Microsoft Office Excel software, a summary of the statistics, including, arithmetic mean, standard deviation, standard error of mean, and range (minimal-maximal value), was calculated for TE contents in CG and TA tissue samples. The difference in the results between two groups of samples were 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 M, standard deviation SD, standard error of mean, and range) of the Ag, Al, As, Au, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Dy, Er, Eu, Fe, Ga, Gd, Hg, Ho, Ir, La, Li, Lu, Mn, Mo, Nb, Nd, Ni, Pb, Pd, Pr, Pt, Rb, Sb, Sc, Se, Sm, Sn, Tb, Te, Th, Ti, Tl, Tm, U, Y, Yb, Zn, and Zr mass fraction in CG and TA tissue samples. The ratios of means and the comparison of mean values of Ag, Al, Au, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Er, Fe, Ga, Hg, La, Li, Mn, Mo, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Sn, Tl, U, Y, Yb, Zn, and Zr mass fractions in CG and TA are presented in Table 2. Table 3 depicts the results of comparison the contents of Ag, Al, Au, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Er, Fe, Ga, Hg, La, Li, Mn, Mo, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Sn, Tl, U, Y, Yb, Zn, and Zrin CG and TA sample groups with those in normal thyroid(from data analysis of previous publications[43,44]), as well as comparison the contents of these ChE in CG and TA sample groups.

Table 1: Measures of central tendency (Mean, SD and range) for 50 trace elements mass fraction (mg/kg, dry mass basis) in thyroid colloid goiter and adenoma.

Element	Colloid nodular goiter (n=46)			Adenoma (n=19)		
	M	SD	Range	M	SD	Range
Ag	0.192	0.214	0.002-0.842	0.181	0.180	0.0012-0.6790
Al	27.1	24.7	6.6-95.1	34.2	24.1	8.7-78.4
As	<0.004	-	-	<0.004	-	-
Au	0.0141	0.0152	0.0030-0.0585	0.0287	0.0293	0.0030-0.0709
B	5.50	17.8	0.9-85.2	3.38	2.74	1.00-7.30
Be	0.00072	0.00053	0.0002-0.0020	0.00181	0.00222	0.00020-0.00600
Bi	0.0585	0.0560	0.0039-0.2140	0.112	0.157	0.0113-0.4220
Cd	1.26	1.30	0.126-5.360	2.78	2.51	0.31-6.39
Ce	0.0186	0.0185	0.0031-0.0696	0.0246	0.0174	0.0073-0.0459
Co	0.0576	0.0282	0.015-0.147	0.0660	0.0469	0.0159-0.1590
Cr	1.18	1.38	0.144-7.300	1.36	0.82	0.259-2.79
Cs	0.0216	0.0232	0.0076-0.1140	0.052	0.085	0.0111-0.205
Dy	<0.005	-	-	<0.005	-	-
Er	0.00299	0.00332	0.0010-0.0138	0.00400	0.00390	0.0010-0.0090
Eu	<0.001	-	-	<0.001	-	-
Fe	449	597	62-2734	571	675	52.3-2563.0
Ga	0.0210	0.0080	0.0100-0.0340	0.0223	0.0097	0.0100-0.0300
Gd	<0.001	-	-	<0.001	-	-
Hg	1.18	1.01	0.10-5.18	1.16	1.26	0.193-5.200
Ho	<0.0002	-	-	<0.0002	-	-
Ir	<0.0003	-	-	<0.0003	-	-
La	0.00990	0.00921	0.0017-0.0356	0.0116	0.0105	0.0054-0.0237
Li	0.0281	0.0117	0.0073-0.0541	0.0401	0.0236	0.0185-0.0680
Lu	<0.0002	-	-	<0.0002	-	-
Mn	1.77	1.13	0.45-5.50	1.67	1.88	0.10-6.12
Mo	0.183	0.121	0.049-0.627	0.233	0.145	0.046-0.448
Nb	<0.013	-	-	<0.013	-	-
Nd	0.0139	0.0087	0.0031-0.0331	0.0141	0.0047	0.0096-0.0190
Ni	2.63	2.43	0.13-10.40	3.95	3.39	0.48-9.00
Pb	0.94	1.86	0.12-8.90	1.86	3.29	0.26-9.30
Pd	<0.012	-	-	<0.012	-	-
Pr	0.00396	0.00359	0.00053-0.01310	0.00475	0.00345	0.0012-0.0093
Pt	<0.0002	-	-	<0.0002	-	-
Rb	9.50	4.23	2.5-22.1	8.96	3.19	3.6-16.4
Sb	0.127	0.113	0.00102-0.42500	0.140	0.117	0.0449-0.4660
Sc	0.0196	0.0316	0.0002-0.1130	0.0286	0.0451	0.0003-0.1400
Se	3.54	3.31	0.86-13.80	3.01	2.43	0.72-10.60
Sm	0.00169	0.00156	0.00040-0.00690	0.00252	0.00263	0.0004-0.0080
Sn	0.0458	0.0384	0.0143-0.1720	0.0756	0.0443	0.0331-0.1570
Tb	<0.0001	-	-	<0.0001	-	-
Te	<0.007	-	-	<0.007	-	-
Th	0.0074	0.0062	0.0020-0.0210	0.0229	0.0293	0.0020-0.0783
Ti	<0.4	-	-	<0.4	-	-
Tl	0.00174	0.00093	0.00052-0.00350	0.00238	0.00164	0.0011-0.0054
Tm	<0.0003	-	-	<0.0003	-	-
U	0.00145	0.00053	0.00082-0.00240	0.00083	0.00035	0.00044-0.00110
Y	0.0113	0.0103	0.0036-0.0346	0.0115	0.0140	0.0031-0.0361
Yb	0.000246	0.000087	0.00020-0.00040	0.000375	0.000236	0.00020-0.00070
Zn	121	51	47-264	129	58	57.7-251.0
Zr	0.074	0.045	0.031-0.205	0.080	0.059	0.031-0.165

Table 2: Differences between mean values (M±SEM) of trace element mass fractions (mg/kg, dry mass basis) in thyroid colloid goiter and adenoma.

Element	Thyroid tissue				Ratio
	Colloid goiter (CG)	Adenoma (TA)	Student's t-test, $p\leq$	U-test, p	CG/TA
Ag	0.192±0.038	0.181±0.050	0.861	>0.05	1.06
Al	27.1±5.3	34.2±9.1	0.516	>0.05	0.79
Au	0.0141±0.0030	0.0287±0.0110	0.247	>0.05	0.49
B	5.50±3.8	3.38±1.12	0.598	>0.05	1.63
Be	0.00072±0.00011	0.00181±0.00090	0.279	>0.05	0.40
Bi	0.0585±0.0130	0.112±0.064	0.450	>0.05	0.52
Cd	1.26±0.28	2.78±0.95	0.167	>0.05	0.45
Ce	0.0186±0.0040	0.0246±0.0090	0.567	>0.05	0.76
Co	0.0576±0.0049	0.0660±0.0135	0.571	>0.05	0.87
Cr	1.18±0.24	1.36±0.24	0.596	>0.05	0.87
Cs	0.0216±0.0050	0.052±0.038	0.467	>0.05	0.42
Er	0.00299±0.00100	0.00400±0.00200	0.580	>0.05	0.75
Fe	449±92	571±174	0.542	>0.05	0.79
Ga	0.0210±0.0020	0.0223±0.0050	0.825	>0.05	0.94
Hg	1.18±0.17	1.16±0.34	0.948	>0.05	1.02
La	0.00990±0.00200	0.0116±0.0060	0.814	>0.05	0.85
Li	0.0281±0.0030	0.0401±0.0100	0.275	>0.05	0.70
Mn	1.77±0.23	1.67±0.54	0.875	>0.05	1.06
Mo	0.183±0.026	0.233±0.055	0.429	>0.05	0.79
Nd	0.0139±0.0020	0.0141±0.0030	0.948	>0.05	0.99
Ni	2.63±0.54	3.95±1.39	0.406	>0.05	0.67
Pb	0.94±0.41	1.86±1.24	0.503	>0.05	0.51
Pr	0.00396±0.00100	0.00475±0.00200	0.695	>0.05	0.83
Rb	9.50±0.50	8.96±0.82	0.815	>0.05	1.06
Sb	0.127±0.019	0.140±0.034	0.749	>0.05	0.91
Sc	0.0196±0.0060	0.0286±0.0140	0.552	>0.05	0.69
Se	3.54±0.56	3.01±0.65	0.548	>0.05	1.18
Sm	0.00169±0.00033	0.00252±0.00099	0.410	>0.05	0.67
Sn	0.0458±0.0090	0.0756±0.0170	0.146	>0.05	0.61
Th	0.0074±0.0010	0.0229±0.0011	0.214	>0.05	0.32
Tl	0.00174±0.00021	0.00238±0.00067	0.391	>0.05	0.73
U	0.00145±0.00022	0.00083±0.00020	0.077	>0.05	1.75
Y	0.0113±0.0030	0.0115±0.0060	0.979	>0.05	0.98
Yb	0.000246±0.000024	0.000375±0.0001 18	0.358	>0.05	0.66
Zn	121±8	129±13	0.577	>0.05	0.94
Zr	0.074±0.010	0.080±0.029	0.846	>0.05	0.93

M – arithmetic mean, SEM – standard error of mean.

DISCUSSION

As was shown before [29,30,35,47-53] good agreement of the 50 TE mass fractions in CRM IAEA H-4, INCT-SBF-4, INCT-TL-1, and INCT-MPH-2 samples determined by both INAA-LLR and ICP-MS methods with the certified data of these CRMs indicates acceptable accuracy of the results obtained in the study of CG and TA samples and presented in Table 1 to Table 3. In general, thee differences found for Ag, Al, Au, Be, Cr, Cs, Hg, Mn, Pb, Rb, Sb, Sc, Th, Yb, Zn, and Zr contents in CG and TA tissue samples were similar in comparison with normal thyroid tissue (Table 3). In affected tissues contents of Ag, Al, Cr, Hg, Mn, Th, and Zn increased, whereas levels of Au, Be, Cs, Pb, Rb, Sb, Sc, Th, Yb, and Zr did not changed in both groups of samples (Table 3). There was not found any differences between TE contents of CG and TA, when results for these groups were compared with each other (Table 2 and Table 3). Published data on comparison of Ag, Al, As, Au, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Dy, Er, Eu, Fe, Ga, Gd, Hg, Ho, Ir, La, Li, Lu, Mn, Mo, Nb, Nd, Ni, Pb, Pd, Pr, Pt, Rb, Sb, Sc, Se, Sm, Sn, Tb, Te, Th, Ti, Tl, Tm, U, Y, Yb, Zn, and Zr levels in CG and TA were not found. Thus, from obtained results it was possible to conclude that the common characteristics of CG and TA tissue samples in comparison with normal thyroid were elevated level of Ag, Al, Cr, Hg, Mn, Th, and Zn. Therefore, it is reasonable to conclude that these TE can be involved in etiology and pathogenesis of such thyroid disorders as CG and TA.

Silver

Ag is a TE with no recognized trace metal value in the human body[56]. Food is the major intake source of Ag and this metal is authorized as a food additive(E174) in the EU[57]. Another source of Agis contact with skin and mucosal surfaces because Ag is widely used in different applications (e.g., Jewelry, wound dressings, or eye drops)[58]. Ag in metal form and inorganic Ag compounds ionize in the presence of water, body fluids or tissue exudates. The silver ion Ag^+ is biologically active and readily interacts with proteins, amino acid residues, free anions and receptors on mammalian and eukaryotic cell membranes[59]. Besides such the adverse effects of chronic exposure to Ag as a permanent

bluish-gray discoloration of the skin (argyria) or eyes (argyrosis), exposure to soluble Ag compounds may produce other toxic effects, including liver and kidney damage, irritation of the eyes, skin, respiratory, and intestinal tract, and changes in blood cells[60].

In experimental studies it was shown that Ag nanoparticles may affect thyroid hormone metabolism[61]. More detailed knowledge of the Ag toxicity can lead to a better understanding of the impact on human health, including thyroid function.

Table 3: Comparison the trace element contents in different pathological transformations of thyroid.

Comparison with:	Normal thyroid*		Colloid Goiter
Element	Colloid Goiter	Adenoma	Adenoma
Ag	↑	↑	=
Al	↑	↑	=
Au	=	=	=
B	=	↑	=
Be	=	=	=
Bi	↑	=	=
Cd	↓	=	=
Ce	↑	=	=
Co	↑	=	=
Cr	↑	↑	=
Cs	=	=	=
Er	↑	=	=
Fe	↑	=	=
Ga	↓	=	=
Hg	↑	↑	=
La	↑	=	=
Li	↑	=	=
Mn	↑	↑	=
Mo	↑	=	=
Nd	↑	=	=
Ni	↑	=	=
Pb	=	=	=
Pr	↑	=	=
Rb	=	=	=
Sb	=	=	=
Sc	=	=	=
Se	↑	=	=
Sm	↑	=	=
Sn	↓	=	=
Th	=	=	=
Tl	↑	=	=
U	↑	=	=
Y	↑	=	=
Yb	=	=	=
Zn	↑	↑	=
Zr	=	=	=

* From analysis of previous publications [43,44],↑ - element content is higher, ↓ - element content is lower, = - no difference

Aluminum

Al is the most prevalent metal in the environment. Environmental media may be contaminated with Al from anthropogenic sources and through the weathering of rocks and minerals[62]. The trace element Al is not described as essential, because there is no biochemical function directly associated with it. Food is the major intake source of Al, followed by drinking water[63]. The additional sources of human exposure to Al are Al-containing food packaging, foils, cooking utensils and baking trays made of Al, cosmetic products (antiperspirants, sun creams, toothpaste) and drugs (antacid agents)[64,65]. The toxic effects of Al lead to oxidative stress, immunologic alterations, genotoxicity, and other disorders, including cell membrane perturbation, apoptosis, necrosis and dysplasia. Furthermore, it has been shown in experimental and epidemiological studies that Al can affect thyroid iodide uptake and hormones secretion[66,67].

Chromium

The general population can be exposed to low levels of Cr primarily through consumption of food and to a lesser degree through inhalation of ambient air and ingestion of drinking water[68].Cr-compounds are cytotoxic, genotoxic, and carcinogenic in nature. Some Cr forms, including hexavalent chromium (Cr^{6+}), are toxicants known for their carcinogenic effect in humans. They have been classified as certain or probable carcinogens by the International Agency for Research on Cancer[69]. The lung cancer risk is prevalent in pigment chromate handlers, ferrochromium production workers, stainless steel welders, and chrome-platers[70]. Except in Cr-related industries and associated environments, Cr intoxication from environmental exposure is not common. However, it was found, that drinking water supplies in many

geographic areas contain chromium in the +3 and +6 oxidation states. Exposure of animals to Cr^{6+} in drinking water induced tumors in the mouse small intestine[71]. Many other animal experiments and *in vitro* studies demonstrate also that Cr can induce oxidative stress and exert cytotoxic effects[72]. Besides reactive oxygen species (ROS) generation, oxidative stress, and cytotoxic effects of Cr exposure, a variety of other changes like DNA damage, increased formation of DNA adducts and DNA-protein cross-links, DNA strand breaks, chromosomal aberrations and instability, disruption of mitotic cell division, chromosomal aberration, premature cell division, S or G2/M cell cycle phase arrest, and carcinogenesis also occur in humans or experimental test systems[70]. Recently, in acase-control study on the association of TE exposure and TBNs it has been shown that Cr is a potential influencing factor for the risk of thyroid tumor and goiter[73].

Mercury

In the general population, potential sources of Hg exposure include the inhalation of this metal vapor in the air, ingestion of contaminated foods and drinking water, and exposure to dental amalgam through dental care[74]. Hg is one of the most dangerous environmental pollutants[75].The growing use of this metal in diverse areas of industry has resulted in a significant increase of environment contamination and episodes of human intoxication. Many experimental, epidemiologic, and occupational studies of Hg in different chemical states shown significant alterations in thyroid hormones metabolism and thyroid gland parenchyma[73,76,77]. Moreover, Hg was classified as certain or probable carcinogen by the International Agency for Research on Cancer[69]. For example, in Hg polluted area thyroid cancer incidence was almost 2 times higher than in adjacent control areas[78].

Manganese

Mnis an essential micronutrient because this TE acts as a co-factor in many enzymatic reactions involved in the metabolisms of lipid, protein, carbohydrate and amino acid, etc.[79]. The diet, natural and anthropogenic contaminated environment are the main sources of Mn exposure in general populations. It was found in many experimental and epidemiologic studies that excessive environmental Mn exposure may affect the balance of thyroid hormone homeostasis via decreasing serum thyroid hormone levels, including T3 and T4[79]. Furthermore, recently, in a case-control study on the association of TE exposure and TBNs it was shown that Cr is a potential influencing factor for the risk of thyroid tumor and goiter[73].

Thorium

Th is a naturally radioactive TE, which effects by its chemical toxicity and radiation on skeleton, nervous and endocrine systems. Environmental contamination by Th, originated mainly from mining activities or spills and contaminated environment is the main source of Th exposure in general populations. The results of many experimental studies indicate that Th administration exerts hazardous effects on the neuroendocrine axis and causes the imbalance of thyroid hormones and structural changes in thyroid gland[80,81]. Moreover, an epidemiologic and clinicopathologic study found an apparent increased prevalence of both benign and malignant thyroid disease in the group of patients treated with Th-contained compound (Thorotrast)[82].

Zinc

Zn, as a trace metal,has structural, catalytic and regulatory roles in normal and pathophysiology. This TE is a constituent of more than 3000 proteins and is a cofactor for over 300 enzymes[83]. Zn is an essential mediator of cell proliferation and differentiation through the regulation of DNA synthesis and mitosis. Zn also affects DNA repair pathways by regulating multiple intracellular signaling pathways and altering proteins involved in DNA maintenance[84]. This metal also maintenance the balance of a cellular redox[85]. Thus, Zn is important cofactors in diverse cellular processes. Concern the thyroid function, Zn is involved in the synthesis of TSH and important for the proper functioning of T3 because T3 nuclear receptors contain Zn ions[86], but for all that, there is a strong negative correlation between serum Zn content and thyroid hormone levels[87]. There are good reasons for such speculations since experimental and epidemiological data support the hypothesis that Zn overload is a risk factor for benign and malignant tumors[84,88-90]. Food and particularly red meat is a main source of Zn intake for humans[91]. In other words, by us in glow or high levels of the TE in affected thyroid tissues researchers try to determine the role of either deficiency or excess of all TE in the etiology and pathogenesis of thyroid diseases. From the results of such studies, it is not alwayspossible to decide whether the measured decrease or increase in TE level in pathologically altered tissue is the cause of the changes or vice versa.

Limitations

This study has several limitations. Firstly, analytical techniques employed in this study measure only fifty TE (Ag, Al, As, Au, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Dy, Er, Eu, Fe, Ga, Gd, Hg, Ho, Ir, La, Li, Lu, Mn, Mo, Nb, Nd, Ni, Pb, Pd, Pr, Pt, Rb, Sb, Sc, Se, Sm, Sn, Tb, Te, Th, Ti, Tl, Tm, U, Y, Yb, Zn, and Zr) mass fractions. Future studies should be directed toward using other analytical methods which will extend the list of TE investigated in normal thyroid and in pathologically altered tissue. Secondly, the sample size of CG group and, particularly, of TA group was relatively small and prevented investigations of TE contents in these groups using differentials like gender, histological types of CG and TA, nodules functional activity, stage of disease, and dietary habits of patients with CG and TA. Lastly, generalization of our results may be limited to Russian population. Despite these limitations, this study provides evidence on TBNs-specific tissue Ag, Al, Cr, Hg, Mn, Th, and Zn level alteration and shows the necessity to continue TE research of TBNs.

CONCLUSIONS

In this work, TE analysis was performed in CG and TA tissue samples using the INAA-LLR non-destructive analytical method and the ICP-MS destructive

analytical method. The combination of these methods has been shown to be a suitable analytical tool for the determination of fifty TE content in the tissue samples of human thyroid in norm and pathology, including needle-biopsy specimens. It was observed that in both CG and TA tissues contents of Ag, Al, Cr, Hg, Mn, Th, and Zn increased, whereas levels of Au, Be, Cs, Pb, Rb, Sb, Sc, Th, Yb, and Zr did not changed in comparison with normal thyroid tissue. It was not found any differences between TE contents of CG and TA.

From the results obtained, it was possible to conclude that the combined characteristics of CG and TA tissue samples were elevated in the level of Ag, Al, Cr, Hg, Mn, Th and Zn in comparison with normal thyroid, and therefore, these TE could be involved in the etiology and pathogenesis of thyroid disorders such as CG and TA.

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AUTHOR'S CONTRIBUTION

Zaichick V: Writing original draft, review, data curation, literature survey, editing, methodology.

DATA AVAILABILITY

Data will be made available on reasonable request.

CONFLICT OF INTEREST

None to declare.

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