Original Research Article

What Trace Elements can beinvolved in Thyroid Hypertrophic and Adenomatous Transformation?

ABSTRACT

Background:Thyroid benign nodules (TBNs) are the most common lesions of this endocrine gland and are prevalent diseases around the world. Among TBNs the colloid goiter (CG) and thyroid adenoma (TA) are very frequentdiseases. An evaluation of the variant of TBNs is clinically importantfor subsequent therapeutic interventions, as well as for more clear understanding the etiology of these disorders. The aim of this exploratory study was to examine differences in the content offifty trace elements (TE)in tissues of CGand TA.

Methods:Thyroid tissue levels of TEwere prospectively evaluated in 46 patients with CG and 19 patients with TA. Measurements were 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 TEanalysis.

Results: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.

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

Keywords: Thyroid; Thyroid colloid goiter; Thyroid adenoma;Traceelements;Neutron activation analysis; Inductively coupled plasma mass spectrometry

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INTRODUCTION

Thyroid benign nodules (TBNs) are the most common lesions of this endocrine gland that encountered globally and frequently discoveredby 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]. An evaluation of the variant ofTBNs is clinically importantfor subsequent therapeutic interventions.For this reason the finding of specific characteristics ofCG and TA is the barest necessity for the differential diagnosis of these thyroid disorders.

For over 20th century, there was the dominant opinion that TBNsis the simple consequence of iodine deficiency. However, it was found that TBNsis a frequent disease even in those countries and regions where the population is never exposed to iodine shortage [4]. Moreover, it was shown thatiodine excess has severe consequences on human health and associated with the presence of TBNs[5-8]. It was also demonstrated that besides the iodine deficiencyand excess many other dietary, environmental, and occupational factors are associated with the TBNsincidence [9-11]. Among these factorsa 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 TEhavealso essential physiological functions [13]. Essential or toxic (goitrogenic, mutagenic, carcinogenic) properties of TEdepend on tissue-specific need or tolerance, respectively [13].Excessive accumulation or an imbalance of the TEmay disturb the cell functions and may result in cellular degeneration, death, benign or malignant transformation [13-15].

In our previous studiesthe 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 levelin the normal thyroid was investigated in relation to age, gender and some non-thyroidal diseases [23,24]. After that, variations ofmanyTE content with age in the thyroid of males and femaleswere studied and age- and gender-dependence of some TEwas observed [25-41]. Furthermore, a significant difference between some TEcontents in CGand TA in comparison with normal thyroid was demonstrated [42-44].

To date,the etiology and pathogenesis of CGand TAhas to be considered as multifactorial. The present study was performed to find differences in TEcontents between CGand TA group of samples, as well as to clarify the role of some TEin the etiology of these thyroid lesions. Having this in mind, our aim was to assess the 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)contents in CG and TAtissue samples 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 (ICP-MS), respectively. A further aim was to compare the levels of these TEin CG and TA group of samples.

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MATERIAL AND METHODS

All patients suffered from CG (n=46, mean age M±SD was 48±12 years, range 30-64) andTA(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. Thick-needle puncture biopsy of suspicious nodules of thethyroid 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 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

All tissue samples were divided into two portions using a titanium scalpel [45]. 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].

The pounded samples weighing about 10 mg (for biopsy) and 100 mg (for resected materials) were used for ChE 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 WWR-c 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, prostate, and scalp hair [29,30,35,47-53].

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-SLRmode optimization was used [55].All thyroid samples were prepared in duplicate, and mean values of TEcontents were used in final calculation. Mean values of TEcontents were used in final calculation for the Ag, Co, Cr, Hg, Rb, Sb, Se, and Zn mass fractions measured by two methods.Using Microsoft Office Excelsoftware, a summary of the statistics, including, arithmetic mean, standard deviation, standard error of mean, and range (minimal - maximal value), was calculated for TEcontents in CGand TAtissue samples.The difference in the results between two groups of sampleswas evaluated by the parametric Student's *t*-test and non-parametricWilcoxon-Mann-Whitney *U*-test.

RESULTS

Table 1 presents certain statistical parameters (arithmetic mean, standard deviation, 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 Zrmass fractionin 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 Zrmass fractions in CG and TAare 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 CGand TAsample groups with those in normal thyroid(from data analysis of previous publications [43,44]), as well as comparison the contents of these ChE in CGand TA sample groups.

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-2samples 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 Tables 1–3.

In a general sense variations found for Ag, Al, Au, Be, Cr, Cs, Hg, Mn, Pb, Rb, Sb,Sc, Th, Yb, Zn, and Zrcontents 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 Zrdid 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 (Tables 2 and 3).

Table 1.Some statistical parameters of 50 trace element mass fraction (mg/kg, dry mass basis) in the thyroid colloid goiter and adenoma

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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

M – arithmetic mean, SD – standard deviation.

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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±0.000118	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.

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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 Zrlevels in CG and TAwere not found.

Thus, from obtained results it was possible to conclude that the common characteristics of CG and TAtissue 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 TEcan 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]. 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 [57]. Besides such the adverse effects of chronic exposure to Agas 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 [58]. In experimental studies it was shown that Ag nanoparticles may affect thyroid hormone metabolism [59]. 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

Comparisonwith:	Normalthyroid*		ColloidGoiter
Element	ColloidGoiter	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

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Aluminum

Al is the most widely distributed metal in the environment. Environmental media may be contaminated by Al from anthropogenic sources and through the weathering of rocks and minerals

[60]. The trace element Al is not described as essential, because no biochemical function has been directly connected to it. Toxic actions of Al induce oxidative stress, immunologic alterations, genotoxicity, and other disorders, including cell membrane perturbation, apoptosis, necrosis and dysplasia [60]. Furthermore, it was shown in experimental and epidemiological studies that Al can affect thyroid iodide uptake and hormones secretion [61,62].

Chromium

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 [63]. The lung cancer risk is prevalent in pigment chromate handlers, ferrochromium production workers, stainless steel welders, and chrome-platers [64]. Except in Cr-related industries and associated environments, Cr intoxication from environmental exposure is not common. However, it was found, that drinking water suppliesin 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 [65]. Many other animal experiments and in vitro studies demonstrate also that Cr can induce oxidative stress and exert cytotoxic effects [66]. 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 [64]. Recently, in acase-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 [67].

Mercury

Hg is one of the most dangerous environmental pollutants [68].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 [67,69,70]. Moreover, Hg was classified as certain or probable carcinogen by the International Agency for Research on Cancer [63]. For example, in Hg polluted area thyroid cancer incidence was almost 2 times higher than in adjacent control areas [71].

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. [72]. The diet, natural and anthropogenic contaminatedenvironment are the main sources of Mnexposure in general populations.It was found in many experimental and epidemiologicstudies that excessive environmental Mn exposure may affect the balance of thyroid hormone homeostasis via decreasing serum thyroid hormone levels, including T3 and T4[72]. 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 [67].

Thorium

Th isa naturally radioactive TE, which effects by its chemical toxicity and radiation on skeleton, nervous and endocrine systems. The results of many experimental studies indicate that Th administration exerts hazardous effects on the neuroendocrine axis andcausesthe imbalance of thyroid hormones and structural changes in thyroid gland [73,74]. Moreover, an epidemiologic and

clinicopathologic study found an apparentincreased prevalence of both benign and malignant thyroid disease in the group of patients treated with Th-contained compound (Thorotrast) [75].

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 [76]. 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 [77]. This metal also maintenance the balance ofa cellular redox [78]. 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 [79]. However, high Zn concentrations are toxic to the cells and the elevated level of Zn mass fractions in thyroid tissue may contribute to harmful effects on the gland. 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 [77,80-82].

Characteristically, elevated or reduced levels of TE observed in thyroid nodules are discussed in terms of their potential role in the initiation and promotion of these thyroid lesions. In other words, using the low or high levels of the TEin affected thyroidtissues researchers try to determine the role of the deficiency or excess of each TEin the etiology and pathogenesis of thyroid diseases.In our opinion, abnormal levels of many TEin TBNscould be and cause, and also effect of thyroid tissuetransformation. From the results of such kind studies, it is not alwayspossible to decide whether the measured decrease or increase in TElevel in pathologically altered tissue is the reason for alterations or vice versa.

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Limitations

This study has several limitations. Firstly, analytical techniques employed in this study measure only fiftyTE(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 TEinvestigated in normal thyroid and in pathologically altered tissue. Secondly, the sample size of CG group and, particularly, ofTAgroup was relatively smalland prevented investigations of TEcontents in thesegroups using differentials like gender, histological types of CG and TA,nodulesfunctional 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 TEresearch ofTBNs.

CONCLUSION

In this work, TEanalysis was carried out in the tissue samples of CG and TAusing non-destructive analytical methodINAA-LLR and destructive analytical method ICP-MS. It was shown that combination of these methodsis an adequate analytical tool for the determination of fiftyTE(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)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 changedin

comparison with normal thyroid tissue.It was not found any differences between TE contents of CG and TA.

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

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CONFLICT OF INTEREST

No conflict of interest associated with this work.

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