RESEARCH ARTICLE

Comparison of Ten Trace Element Contents in Thyroid Goiter, Adenoma, and Thyroiditis investigated using Neutron Activation Analysis

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ABSTRACT

Purpose: Thyroid benign nodules (TBNs) are the most common lesions of this endocrine gland. Among TBNs the colloid goiter (CG), thyroiditis (T), and thyroid adenoma (TA) are the most frequentdiseases. An evaluation of the variant of TBNs is clinically important for 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 ofsilver (Ag), cobalt (Co), chromium (Cr), iron (Fe), mercury (Hg), rubidium (Rb), antimony (Sb), scandium (Sc), selenium (Se), and zinc (Zn) in tissues of CG, TA, and T. **Methods:** Thyroid tissue levels of ten trace elements (TE)were prospectively evaluated in 46 patients with CG, 19 patients with TA, and 12 patients with thyroiditis. Measurements were performed using non-destructive instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides. 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 CG, TA and T tissues content of Ag and Hg was significantly higher than in normal thyroid tissue, but there were no differences in these TE contents among all kind of TBNs investigated in the study. Rb was TE, which accumulation in T tissue was higher, whereas Se and Zn levels were lower than in CG, and TA. **Conclusion:** The abnormal increase in Ag and Hg level in all TBNs, as well as the increase in levels of Rb and the decrease content of Se and Zn in thyroid with T might demonstrate an involvement of these TE in etiology and pathogenesis of TBNs. It was supposed that elevated level of Rb and reduced levels of Se and Zn in thyroid affected tissue can be used as thyroiditis marker.

Key words: Thyroid, Thyroid colloid goiter, Thyroid adenoma, Thyroiditis, Trace elements, Instrumental neutron activation analysis

INTRODUCTION

Thyroid benign nodules (TBNs) are the most common lesions of this endocrine gland that encountered globally and frequently discovered by palpation during a physical examination, or incidentally, during clinical imaging procedures. TBNs include non-neoplastic lesions (different kinds of thyroid goiter, thyroiditis, and cysts) and neoplastic lesion such as thyroid adenoma. Among TBNs the colloid goiter (CG), thyroiditis (T), and thyroid adenoma (TA) are the most frequent diseases [1-3]. An evaluation of the variant of TBNs is clinically important for subsequent therapeutic interventions. For this reason the finding of specific characteristics of various TBNs is the barest necessity for the differential diagnosis of these thyroid disorders.

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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 TBNs incidence [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 have 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]. Furthermore, a significant difference between some TE contents in CG, TA, and T in comparison with normal thyroid was demonstrated [42-46].

To date, the etiology and pathogenesis of TBNs has to be considered as multifactorial. The present study was performed to find differences in TE contents between CG, TA, and T group of samples, as well as to clarify the role of some TE in the TBNsetiology. Having this in mind, our aim was to assess the silver (Ag), cobalt (Co), chromium (Cr), iron (Fe), mercury (Hg), rubidium (Rb), antimony (Sb), scandium (Sc), selenium (Se), and zinc (Zn) contents in CG, TA, and Tissue using non-destructive instrumental neutron activation analysis with high resolution spectrometry of long-lived radionuclides(INAA-LLR). A further aim was to compare the TE levels of CG, TA, and T groups of samples among themselves.

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/ornational research committee and with the 1964 Helsinki declaration and its later amendments, or with comparable ethical standards.

MATERIAL AND METHODS

All patients suffered from CG (n=46, mean age M±SD was 48±12 years, range 30-64), TA (n=19, mean age M±SD was 41±11 years, range 22-55), and T (mean age M±SD was 39±9 years, range 34-50) were hospitalized in the Head and Neck Department of the Medical Radiological Research Centre. The group of patients with T included 8 persons with Hashimoto's thyroiditis and 6 persons with Riedel's Struma. 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/histological results obtained during studies of biopsy and resected materials.

All tissue samples were divided into two portions using a titanium scalpel [47]. 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 [48]. The pounded sample weighing about 10 mg (for biopsy) and 50 mg (for resected materials) was used for TE measurement by INAA-LLR.

To determine contents of the TE by comparison with a known standard, biological synthetic standards (BSS) prepared from phenol-formaldehyde resins were used [49]. In addition to BSS, aliquots of commercial, chemically pure compounds were also used as standards. Ten certified reference material IAEA H-4 (animal muscle) and IAEA HH-1 (human hair) sub-samples weighing about 50 mg were treated and analyzed in the same conditions that thyroid samples to estimate the precision and accuracy of results.

A vertical channel of nuclear reactor was applied to determine the content of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn by INAA-LLR. Details of used nuclear reactions, radionuclides, gamma-energies, spectrometric unit, sample preparation and procedure of measurement were presented in our earlier publications concerning the INAA of TE contents in human thyroid, prostate and scalp hair [29, 30, 50, and 51].

A dedicated computer program for INAA mode optimization was used [52]. 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, and 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 CG, TA, and Tissue samples. The difference in the results between three groups of samples (CG, TA, and T) was evaluated by the parametric Student's *t*-test and non-parametric Wilcoxon-Mann-Whitney *U*-test.

RESULTS

Table 1 presents certain statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, percentiles with 0.025 and 0.975 levels) of the Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn mass fractionin CG, TA, and T groups of tissue samples.

The ratios of means and the comparison of mean values of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn mass fractions in pairs of sample groups such as CG and TA, CG and T, and TA and Tare presented in Table 2, 3, and 4, respectively.

Table 5 depicts the results of comparison the contents of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn in CG, TA, and T sample groups with those in normal thyroid [43-46], as well as comparison the contents of these TE in CG, TA, and T sample groups among themselves.

DISCUSSION

As was shown before [29,30,50,51] good agreement of the Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn contents in CRM IAEA H-4 and IAEA HH-1 samples analyzed by INAA-LLR with the certified data of this CRM indicates acceptable accuracy of the results obtained in the study of CG, TA, and T samples presented in Tables (1–5).

In a general sense variations found for Br, Cr, Hg, and Zn contents during the goitrous and adenomatous transformations of thyroid were very similar (Table 5). The contents all these TE in goitrous and adenomatous thyroid were higher in comparison with normal gland (Table 5). There was not

Table 1: Some statistical parameters of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn mass fraction (mg/kg, dry mass basis) in thyroid colloid goiter, adenoma and thyroiditis

Tissue	Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Goiter	Ag	0.226	0.236	0.042	0.0020	0.874	0.160	0.0020	0.849
n=46	Co	0.0627	0.0287	0.0050	0.0150	0.147	0.0623	0.0215	0.128
	Cr	0.849	0.834	0.150	0.135	3.65	0.540	0.142	2.88
	Fe	340	332	52	62.0	1350	197	68.8	1344
	Hg	0.987	0.726	0.124	0.0817	3.01	0.920	0.0968	2.36
	Rb	8.85	4.18	0.64	1.00	22.1	8.50	2.53	16.6
	Sb	0.146	0.121	0.021	0.0102	0.425	0.103	0.0128	0.419
	Sc	0.0130	0.0201	0.0040	0.0002	0.0910	0.0058	0.0002	0.0701
	Se	3.09	2.59	0.44	0.994	12.6	2.37	1.16	12.1
	Zn	121	53.4	8.2	47.0	278	109	49.1	269
Adenoma	Ag	0.211	0.201	0.056	0.0115	0.679	0.198	0.0124	0.627
n=19	Co	0.0673	0.0485	0.0140	0.0083	0.159	0.0478	0.0104	0.149
	Cr	1.40	0.85	0.25	0.259	2.79	1.25	0.265	2.70
	Fe	417	419	112	52.3	1407	316	53.3	1357
	Hg	0.796	0.522	0.145	0.149	1.72	0.817	0.162	1.65
	Rb	8.73	3.26	0.84	2.40	16.4	8.60	3.42	15.0
	Sb	0.149	0.124	0.036	0.0449	0.466	0.105	0.0449	0.419
	Sc	0.0174	0.0273	0.0090	0.0003	0.0900	0.0060	0.0003	0.0759
	Se	2.36	0.90	0.24	0.720	3.57	2.25	0.929	3.52
	Zn	128	51	13	48.0	251	135	52.9	225
Thyroiditis	Ag	0.274	0.131	0.066	0.138	0.408	0.274	0.142	0.404
n=14	Co	0.0535	0.0527	0.0068	0.0321	0.0699	0.0512	0.0337	0.0696
	Cr	0.697	0.764	0.342	0.0750	1.88	0.396	0.0778	1.79
	Fe	237	213	62	94.0	797	139	96.2	709

	Hg	0.972	0.494	0.221	0.466	1.68	0.894	0.479	1.64
	Rb	12.7	5.1	1.5	3.80	20.3	12.5	4.68	20.0
	Sb	0.096	0.036	0.016	0.0377	0.126	0.113	0.0424	0.125
	Sc	0.019	0.024	0.011	0.00020	0.0550	0.0091	0.00021	0.0525
	Se	1.82	0.45	0.20	1.15	2.34	1.88	1.20	2.32
	Zn	91.5	29.3	8.5	50.0	140	90.5	52.2	136

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: Differences between mean values (M±SEM) of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn mass fraction (mg/kg, dry mass basis) in thyroid colloid goiter and thyroid adenoma

Element	Thyroidtissue				Ratio
	Goiter n=46	Adenoman=19	Student's t-test *p*≤	U-test *p*	GoitertoAdenoma
Ag	0.226±0.042	0.211±0.056	0.824	>0.05	1.07
Co	0.0627±0.0050	0.0673±0.0140	0.767	>0.05	0.93
Cr	0.849±0.150	1.40±0.25	0.069	>0.05	0.61
Fe	340±52	417±112	0.541	>0.05	0.82
Hg	0.987±0.124	0.796±0.145	0.327	>0.05	1.24
Rb	8.85±0.64	8.73±0.84	0.908	>0.05	1.01
Sb	0.146±0.021	0.149±0.036	0.949	>0.05	0.98
Sc	0.0130±0.0040	0.0174±0.0090	0.647	>0.05	0.75
Se	3.09±0.44	2.36±0.24	0.155	>0.05	1.31
Zn	121±8.2	128±13	0.661	>0.05	0.95

M – arithmetic mean, SEM – standard error of mean

Table 3: Differences between mean values (M±SEM) of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn mass fraction (mg/kg, dry mass basis) in thyroid colloid goiter and thyroiditis

Element	Thyroidtissue				Ratio
	Goiter n=46	Thyroiditis n=14	Student's t-test *p*≤	U-test*p*	GoitertoThyroiditis
Ag	0.226±0.042	0.274±0.066	0.566	>0.05	0.82
Co	0.0627±0.0050	0.0535±0.0068	0.300	>0.05	1.17
Cr	0.849±0.150	0.697±0.342	0.698	>0.05	1.22
Fe	340±52	237±62	0.215	>0.05	1.43
Hg	0.987±0.124	0.972±0.221	0.956	>0.05	1.02
Rb	8.85±0.64	12.7±1.5	**0.030**	**≤0.01**	0.70
Sb	0.146±0.021	0.096±0.016	0.074	>0.05	1.52
Sc	0.0130±0.0040	0.019±0.011	0.623	>0.05	0.68
Se	3.09±0.44	1.82±0.20	**0.014**	**≤0.01**	1.70
Zn	121±8.2	91.5±8.5	**0.017**	**≤0.01**	1.32

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

Table 4: Differences between mean values (M±SEM) of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn mass fraction (mg/kg, dry mass basis) in thyroid adenoma and thyroiditis

Element	Thyroidtissue				Ratio
	Adenoma n=19	Thyroiditis n=14	Student's t-test *p*≤	U-test *p*	AdenomatoThyroiditis
Ag	0.211±0.056	0.274±0.066	0.486	>0.05	0.77
Co	0.0673±0.0140	0.0535±0.0068	0.390	>0.05	1.26
Cr	1.40±0.25	0.697±0.342	0.131	>0.05	2.01
Fe	417±112	237±62	0.175	>0.05	1.76
Hg	0.796±0.145	0.972±0.221	0.525	>0.05	0.82
Rb	8.73±0.84	12.7±1.5	**0.032**	**≤0.01**	0.69
Sb	0.149±0.036	0.096±0.016	0.204	>0.05	1.55
Sc	0.0174±0.0090	0.019±0.011	0.920	>0.05	0.92
Se	2.36±0.24	1.82±0.20	0.107	**≤0.05**	1.30
Zn	128±13	91.5±8.5	**0.029**	**≤0.01**	1.40

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

Table 5: Comparison the contents of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn in different pathological transformation of thyroid

Comparisonwith:	Normalthyroid*			ColloidGoiter		Adenoma
Element	Goiter	Adenoma	Thyroiditis	Adenoma	Thyroiditis	Thyroiditis
Ag	↑	↑	↑	=	=	=
Co	↑	=	=	=	=	=
Cr	↑	↑	=	=	=	=
Fe	↑	=	=	=	=	=
Hg	↑	↑	↑	=	=	=
Rb	↑	=	↑	=	↑	↑
Sb	=	=	=	=	=	=
Sc	↑	=	=	=	=	=
Se	=	=	=	=	↓	↓
Zn	↑	↑	=	=	↓	↓

* From analysis of previous publications [43-46],↑ - element content is higher, ↓ - element content is lower, = - no difference

found any differences between TE contents of CG and TA (Table 2 and 5).

The variations found for Rb, Se, and Zn in thyroid with Twere some differ than the variations of these TE in CG and TA tissues. In thyroid with T the Rb content was higher, while Se and Zn levels were lower in comparison with CG and TA tissues (Table 3-5).

In this study, content of Ag, Co, Cr, Fe, Hg, Sb, and Scin goitrous thyroid were compared with those from adenomatous thyroids and from thyroid with thyroiditis.

Published data on comparison of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn levels in the different thyroid lesions such as CG, TA and T were not found.

Thus, from obtained results it was possible to conclude that the common characteristics of CG, TA and T samples were elevated contents of Ag and Hg in comparison with normal thyroid and, therefore, these TE may be involved in etiology or pathogenesis of such thyroid disorders as CG, TA and T. Specific characteristics of T tissue among other TBNs is elevated level of Rb and reduced levels of Se and Zn.

Silver

Ag is a TE with no recognized trace metal value in the human body [53]. 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 [54]. Besides such the adverse effects of chronic exposure to A gas 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 [55]. Experimental studies shown that Ag nano particles may affect thyroid hormone metabolism [56]. More detailed knowledge of the Ag toxicity can lead to a better understanding of the impact on human health, including thyroid function.

Mercury

Hg is one of the most dangerous environmental pollutants [57]. 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 and occupational studies of Hg in different chemical states shown significant alterations in thyroid hormones metabolism and thyroid gland parenchyma [58, 59]. Moreover, Hg was classified as certain or probable carcinogen by the International Agency for Research on Cancer [60]. For example, in Hg polluted area thyroid cancer incidence was almost 2 times higher than in adjacent control areas [61].

Rubidium

Rb was only TE, which accumulation in T tissue was higher than in normal thyroid, CG, and TA (Tables 2-5). There is very little information about Rb effects on thyroid function. Rb as a monovalent cation Rb+ is transfered through membrane by the Na+K+-ATPase pump like K+ and concentrated in the intracellular space of cells. Thus, Rb seems to be more intensivly concentrated in the intracellular space of cells during thyroiditis in comparison with normal thyroid cells, and ceels transformed by CG and TA. The sourse of Rb elevated level in T tissue may be Rb environment overload. The excessive Rb intake may result a replacement of medium potassium by Rb, which effects on iodide transport and iodoaminoacid synthesis by thyroid [62]. The sourse of Rb increase in T tissue may be not only the excessive intake of this TE in organism from the environment, but also changed Na+K+ -ATPase or H+K+ -ATPase pump membrane transport systems for monovalent cations, which can be stimulated by endocrin system, including thyroid hormones [63]. It was found also that Rb has some function in immune responce [64] and that elevated concentration of Rb could modulate proliferative responses of the cell, as was shown for bone marrow leukocytes [65]. These data partially clarify the possible role of Rb in etiology and pathogenesis of thyroiditis. Moreover, the significantly elevated level of Rbin thyroid with T could possibly be explored for differential diagnosis of this thyroid disorder from other binighn thyroid nodules.

Selenium

SeasTE is essential for the functioning of many enzymes (selenoproteins) involved in the synthesis and metabolism of thyroid hormones and protection against oxidative damage (such as iodothyronine deiodinases, thioredoxin reductases and glutathione peroxidases) [66]. In fact, compared to other organs, the thyroid gland has a high concentration of Se [66]. Se deficiency among patients with TBNs was observed in many studies [67]. In spite of the fact that low Se status correlates with risk of TBNs, it is important to point out that, like I,Se excess is also not good for health [67].

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 [68]. 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 [69]. This metal also maintenance the balance of a cellular redox [70]. 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 [67]. 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 [69, 71-73].

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 TE in affected thyroid tissues researchers try to determine the role of the deficiency or excess of each TE in the etiology and pathogenesis of thyroid diseases. In our opinion, abnormal levels of many TE in TBNs 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.

Limitations

This study has several limitations. Firstly, analytical techniques employed in this study measure only tenTE (Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn) 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 and T groups was relatively small and prevented investigations of TE contents in these groups using differentials like gender, histological types of CG, TA and T, nodules functional activity, stage of disease, dietary habits of patients with CG, TA and T. Lastly, generalization of our results may be limited to Russian population. Despite these limitations, this study provides evidence on TBNs-specific tissue Ag, Hg, Rb, Se, and Zn level alteration and shows the necessity to continue TE research of benign thyroid nodules. Furthermore, our findings show that mass fraction of Rb is significantly higher, while Se and Zn levels are lower in T as compared to CG and TA tissues (Tables 3, 4, and 5). Thus, it is plausible to assume that levels of these TE in thyroid nodules can be used as T markers. However, this subjects needs in additional studies.

CONCLUSION

In this work, TE analysis was carried out in the tissue samples of benign thyroid nodules using INAA-LLR. It was shown that INAA-LLRis an adequate analytical tool for the non-destructive determination of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn content in the tissue samples of human thyroid in norm and pathology, including needle-biopsy specimens. It was observed that in CG, TA and Ttissues content of Ag and Hg was significantly higher than in normal thyroid tissue, but there were no differences in these TE contents among all kind of TBNs investigated in the study. Rb was TE, which accumulation in T tissue was higher, whereas Se and Zn levels were lower than in CG, and TA. In our opinion, the abnormal increase in Ag and Hg level in all TBNs, as well as the increase in levels of Rb and the decrease content of Se and Zn in thyroid with Tmight demonstrate an involvement of these TE in etiology and pathogenesis of TBNs. It was supposed that elevated level of Rb and reduced levels of Se and Zn in thyroid affected tissue can be used as thyroiditismarker.

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