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Research Article

Possible Role of Inadequate Quantities of Intra-Thyroidal Bromine, Calcium and Magnesium in the Etiology of Female Subclinical Hypothyroidism

Zaichick Vladimir[1]* and Zaichick Sofia[2]

[1]*Radionuclide Diagnostics Department, Medical Radiological Research Centre, Russia*

[2]*Laboratory of Dr. Gabriela Caraveo Piso, Feinberg School of Medicine, Northwestern University, USA*

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***Corresponding author:** V Zaichick, Medical Radiological Research Centre, Korolyev St.4, Obninsk 249036, Kaluga Region, Russia, Tel: (48439) 60289; Fax: (495) 956 1440; Email: vezai@obninsk.com/vzaichick@gmail.com

Abstract

Objective: Subclinical hypothyroidism does affect fertility. The prevalence of subclinical hypothyroidism is 10-15 times more common in women than in men. Many chemical elements play important role in thyroid function and fertility. The aim of this exploratory study was to evaluate whether significant differences of chemical element contents exist between female and male thyroids and how they can be related to the etiology of subclinical hypothyroidism.

Methods: Thyroid tissue levels of Br, Ca, Cl, I, K, Mg, Mn, and Na were prospectively evaluated in 105 healthy persons (33 females and 72 males). Tissue samples were used for chemical element measurements, employing instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides.

Results: It was found that the Br thyroid content of females was significantly higher than that of males, while the Ca and Mg contents were lower.

Conclusion: Inappropriate content of intra-thyroidal Br, Ca and Mg can be associated with the etiology of female subclinical hypothyroidism.

Keywords: Subclinical hypothyroidism; Female Thyroid; Chemical Elements; Neutron activation analysis

Introduction

Adequate thyroid function is important to maintain normal reproduction, because thyroid dysfunction affects fertility in various ways resulting in abnormal ovulatory cycles, luteal phase defects, high prolactin levels, and sex hormone imbalances [1,2]. Therefore, normal thyroid function is necessary for fertility, and to sustain a healthy pregnancy [2]. From large population studies, which measured thyroid function, and systematic reviews of this subject carried out in the 1990s to 2010s, it is known that untreated hypothyroidism is a common condition all over the world [2-11]. The prevalence of subclinical hypothyroidism (SCH) is between 1% and 10% in different countries [2-11] and almost everywhere it is 10-15 times more common in women than in men [4,10]. Form such a great gender-related difference in the prevalence of SCH arises a question about a specific sensitivity of female thyroid tissue to some external and internal factors.

Although the etiology of SCH and other thyroidal disorders is unknown in detail, several risk factors including deficiency or excess of such micronutrients as iodine (I) has been well identified [12-23]. Besides I involved in thyroid function, other chemical elements (ChE) also play important roles such as stabilizers, structural elements, maintenance and regulation of cell function, gene regulation, enzyme cofactors, activation or inhibition of enzymatic reactions, normal peripheral utilization of thyroid hormones and regulation of cell membrane function [24]. Essential or toxic properties of ChE depend on tissue-specific need or tolerance, respectively [25]. Both ChE deficiencies as well as overexposures may disturb the thyroidal cell functions [25]. Moreover, each individual ChE affects the homeostasis of other ChE as some of them share and compete for specific protein transporters and binding proteins, such as metallothioneins. The effect of these interactions can be synergistic or antagonistic. Therefore, besides measuring only total amounts of ChE, the interrelationship of ChE should be taken into account to allow for a more comprehensive description of the ChE impact on thyroid health status.

The reliable data on ChE mass fractions in normal human thyroid separately for female and male gland is apparently extremely limited. There are a few studies regarding ChE content in human thyroid, using chemical techniques and instrumental methods [26-37]. However, the majority of these data are based on measurements of processed tissue and in many studies tissue samples are ashed before analysis. In other cases, thyroid samples are treated with solvents (distilled water, ethanol etc) and then are dried at a high temperature for many hours. There is evidence that certain quantities of ChE are lost as a result of such treatment [38-40]. Moreover, only a few of these studies employed quality control using certified/standard reference materials (CRM/SRM) for determination of the ChE mass fractions. Sample-nondestructive technique such as instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR) is good alternatives for multi-element determination in the samples of thyroid parenchyma.

This work had three aims. The primary purpose of this study was to determine reliable values for such ChE as bromine (Br), calcium (Ca), chlorine (Cl), iodine (I), potassium (K), magnesium (Mg), manganese (Mn), and sodium (Na) contents in intact (normal) thyroid gland of apparently healthy persons using INAA-SLR analysis. The second aim was to compare the levels of ChE in the thyroid tissue of females and males. The final aim was to find and compare the inter-correlations of ChE in normal thyroid of females and males. All studies were approved by the Ethical Committees of the Medical Radiological Research Centre, Obninsk.

Material and Methods

Samples of the human thyroid were obtained from randomly selected autopsy specimens of 33 females (European-Caucasian, aged 3.5 to 87 years) and 72 males (European-Caucasian, aged 2.0 to 80 years). All the deceased were citizens of Obninsk and had undergone routine autopsy at the Forensic Medicine Department of City Hospital, Obninsk. Age ranges for subjects were divided into two age groups, with group 1 (>40 years), and group 2 (>40 years). For females in group 1 (n=11) mean age (±standard error of mean, SEM) was 30.9±3.1 years and in group 2 (n=22) mean age was 66.3±2.7 years. For males in group 1 (n=36) mean age was 22.5±1.4 years and in group 2 (n=36) mean age was 52.4±2.4 years. These groups were selected to reflect the condition of thyroid tissue in the children, teenagers, young adults and first period of adult life (group 1) and in the second period of adult life as well as in old age (group 2). The available clinical data were reviewed for each subject. None of the subjects had a history of an intersex condition, endocrine disorder, or other chronic disease that could affect the normal development of the thyroid. None of the subjects were receiving medications or used any supplements known to affect thyroid trace element contents. The typical causes of sudden death of most of these subjects included trauma or suicide and also acute untreated illness (cardiac insufficiency, stroke, embolism of pulmonary artery, alcohol poisoning).

All right lobes of thyroid glands were divided into two portions using a titanium scalpel [41]. One tissue portion was reviewed by an anatomical pathologist while the other was used for the ChE content determination. A histological examination was used to control the age norm conformity as well as the unavailability of microadenomatosis and latent cancer. After the samples intended for ChE analysis were weighed, they were freeze-dried and homogenized [42-44]. The pounded sample weighing about 100 mg was used for chemical element measurement by INAA-SLR. The samples for INAA-SLR were sealed separately in thin polyethylene films washed beforehand with acetone and rectified alcohol. The sealed samples were placed in labeled polyethylene ampoules.

To determine contents of the elements by comparison with a known standard, biological synthetic standards (BSS) prepared from phenol-formaldehyde resins were used [45]. In addition to BSS, aliquots of commercial, chemically pure compounds were also used as standards. Ten certified reference material (CRM) IAEA H-4 (animal muscle) sub-samples weighing about 100 mg were treated and analyzed in the same conditions that thyroid samples to estimate the precision and accuracy of results.

The content of Br, Ca, Cl, I, K, Mg, Mn, and Na were determined by INAA-SLR using a horizontal channel equipped with the pneumatic rabbit system of the WWR-c research nuclear reactor. The neutron flux in the channel was 1.7×10^{13}ncm^{-2}s^{-1}. Ampoules with thyroid tissue samples, SSB, intralaboratory-made standards, and certified reference material were put into polyethylene rabbits and then irradiated separately for 180s. Copper foils were used to assess neutron flux. The measurement of each sample was made twice, 1 and 120min after irradiation. The duration of the first and second measurements was 10 and 20min, respectively. A coaxial 98-cm^3 Ge (Li) detector and a spectrometric unit (NUC 8100), including a PC-coupled multichannel analyzer, were used for measurements. The spectrometric unit provided 2.9keV resolution at the ^{60}Co 1,332-keV line. Details of used nuclear reactions, radionuclides, and gamma-energies were presented in our earlier publications concerning the INAA chemical element contents in human prostate and scalp hair [46-49].

A dedicated computer program for INAA mode optimization was used [50]. All thyroid samples were prepared in duplicate, and mean values of ChE 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 ChE contents in thyroid tissue samples of females and males. The difference in the results between females and males (age group 1 and 2 combined), as well as between females and males separately in age group 1 and group 2 was evaluated by the parametric Student's t-test and non-parametric Wilcoxon-Mann-Whitney U-test.

Results

Table 1: Neutron activation analysis data of chemical element contents in the IAEA H-4 (animal muscle) reference material compared to certified values (mg/kg, dry mass basis).

Element	This work results	Certified values		
	Mean±SD	Mean	95% confidence interval	Type
Br	5.0±0.9	4.1	3.5 – 4.7	N
Ca	238±59	188	163 – 213	N
Cl	1950±230	1890	1810 – 1970	N
I	<1.0	0.08	-	N
K	16200±3800	15800	15300 – 16400	C
Mg	1100±190	1050	990 – 1110	C
Mn	0.55±0.11	0.52	0.48 – 0.55	C
Na	2190±140	2060	1930 – 2180	C

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

Table 1 depicts our data for eight ChE in ten sub-samples of CRM IAEA H-4 (animal muscle) and the certified values of this material. Table 2 presents certain statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, percentiles with 0.025 and 0.975 levels) of the Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction in normal thyroid tissue of female and male. The comparison of our results with published data for Br, Ca, Cl, I, K, Mg, Mn, and Na mass fraction in normal human thyroid is shown in Table 3. The ratios of means and the difference between mean values of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions in normal thyroid of females and males are presented in Table 4. Because, in our previous studies age-dependents of many ChE in thyroid gland was found [51-54], the comparison between ChE contents in thyroid of females and males separately in age group 1 and in age group 2 was also performed (Tables 5 & 6). The data of inter-correlation calculations (values of r – coefficient of correlation) including all ChE identified by us in thyroid of females and males separately are presented in Table 7.

Table 2: Some statistical parameters of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions (mg/kg, dry mass basis) in normal thyroid tissue of females and males.

Gender	Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Males	Br	13.7	7.8	1.0	1.90	32.3	10.2	2.50	30.7
n=72	Ca	1703	1048	131	414	6230	1470	452	4163
	Cl	3449	1450	219	1030	5920	3470	1262	5657
	I	1786	940	118	220	4205	1742	239	3808
	K	6289	2594	329	2440	14300	5670	2622	12670
	Mg	306	143	19	99.0	930	287	107	572
	Mn	1.31	0.49	0.07	0.510	2.30	1.30	0.534	2.21
	Na	6820	1781	214	3050	13453	6680	3861	11350
Females	Br	22.4	16.1	3.2	5.00	66.9	16.3	5.00	59.2
n=33	Ca	1663	570	198	461	3640	1170	670	3600
	Cl	3317	1480	290	1200	6000	3375	1388	5906
	I	1956	1199	219	114	5061	1562	309	4662
	K	5395	3245	723	1740	13700	4835	2120	13230
	Mg	212	97	24	66.0	364	215	67.5	356
	Mn	1.50	0.84	0.22	0.550	4.18	1.37	0.603	3.41
	Na	6421	1721	320	3800	10450	6700	4122	9924

Mean – arithmetic mean, SD – standard deviation, SEM – standard error of mean, Min – minimum value, Max – maximum value, P 0.025 – percentile with 0.025 level, P 0.975 – percentile with 0.975 level.

Table 3: Median, minimum and maximum value of means of Br, Ca, Cl, I, K, Mg, Mn, and Na contents in normal human thyroid according to data from the literature in comparison with our results (mg/kg, dry mass basis).

Element	This work	Published data [Reference]		
	Females and males (combined) M±SD	Median of means(n)*	Minimum of means M or M±SD, (n)**	Maximum of means M or M±SD, (n)**
Br	16.3±11.6	18.1 (11)	5.12 (44) [26]	284±44 (14) [27]
Ca	1692±1022	1600 (17)	840±240 (10) [28]	3800±320 (29) [28]
Cl	3400±1452	6800 (5)	804±80 (4) [29]	8000 (-) [30]
I	1841±1027	1888 (95)	159±8 (23) [31]	5772±2708 (50) [32]
K	6071±2773	4400 (17)	46.4±4.8 (4) [29]	6090 (17) [33]
Mg	285±139	390 (16)	3.5 (-) [34]	840±400 (14) [35]
Mn	1.35±0.58	1.82 (36)	0.44±11 (12) [36]	69.2±7.2 (4) [29]
Na	6702±1764	8000 (9)	438 (-) [37]	10000±5000 (11) [35]

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

Table 4: Differences between mean values (M±SEM) of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions (mg/kg, dry mass basis) in normal thyroid tissue of males and females.

	Thyroid tissue				Ratio
	Males 2.0-80 years n=72	Females 3.5-87 years n=33	Student's t-test p≤	U-test p	Females to Males
Br	13.7±1.0	22.4±3.2	0.0151	≤0.01	1.64
Ca	1703±131	1663±198	0.864	>0.05	0.98
Cl	3449±219	3317±290	0.718	>0.05	0.96
I	1786±118	1956±219	0.497	>0.05	1.10
K	6289±329	5395±723	0.271	>0.05	0.86
Mg	306±19	212±24	0.0046	≤0.01	0.69
Mn	1.31±0.07	1.50±0.22	0.440	>0.05	1.15
Na	6820±214	6421±320	0.304	>0.05	0.94

M-arithmetic mean, SEM – standard error of mean, t-test - Student's t-test, U-test - Wilcoxon-Mann-

Table 5: Differences between mean values (M±SEM) of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions (mg/kg, dry mass basis) in normal thyroid tissue of males and females aged ≤40 years.

Element	Thyroid tissue				Ratio
	Males (MG1) n=44	Females (FG1) n=11	Student's t-test p≤	U-test p	FG1/MG1
Br	12.5±1.3	13.3±2.5	0.793	>0.05	1.06
Ca	1484±90	1052±65	0.0004	≤0.01	0.71
Cl	3236±314	4109±544	0.190	>0.05	1.27
I	1601±146	1876±346	0.476	>0.05	1.17
K	6549±386	5379±1101	0.340	>0.05	0.82
Mg	309±19	212±39	0.048	≤0.01	0.69
Mn	1.46±0.09	1.43±0.13	0.816	>0.05	0.98
Na	6845±271	5969±458	0.121	>0.05	0.87

M– arithmetic mean, SEM – standard error of mean, t-test - Student's t-test, U-test - Wilcoxon-Mann

Table 6: Differences between mean values (M±SEM) of Br, Ca, Cl, I, K, Mg, Mn, and Na mass fractions (mg/kg, dry mass basis) in normal thyroid tissue of males and females aged >40 years.

Element	Thyroid tissue				Ratio
	Males (MG2) n=28	Females (FG2) n=22	Student's t-test p≤	U-test p	FG2/MG2
Br	15.4±1.7	26.8±4.3	0.021	≤0.01	1.74
Ca	2003±278	2029±276	0.948	>0.05	1.01
Cl	3662±305	2965±318	0.122	>0.05	0.81
I	2048±190	2002±288	0.895	>0.05	0.98
K	5929±577	5408±1013	0.661	>0.05	0.91
Mg	301±39	212±31	0.085	≤0.05	0.70
Mn	1.11±0.08	1.57±0.46	0.359	>0.05	1.41
Na	6784±355	6025±414	0.772	>0.05	0.89

M – arithmetic mean, SEM – standard error of mean, t-test - Student's t-test, U-test - Wilcoxon-Mann-Whitney U-test.

Table 7: Intercorrelations of the chemical element mass fractions in the normal thyroid of females and males (r – coefficient of correlation).

Gender	Element	Br	Ca	Cl	I	K	Mg	Mn	Na
Male	Br	**1.00**	0.06	-0.26[a]	0.05	0.03	-0.08	0.09	-0.08
	Ca	0.06	**1.00**	-0.19	0.08	-0.21	0.30[a]	0.03	-0.17
	Cl	-0.26a	-0.19	**1.00**	0.08	-0.46[b]	0.09	-0.19	0.53[c]
	I	0.05	0.081	0.08	**1.00**	-0,20	-0.21	-0.14	-0.10
	K	0.03	-0.21	-0.46b	-0,20	**1.00**	0.27[a]	-0.05	0.08
	Mg	-0.08	0.30[a]	0.09	-0.21	0.27[a]	**1.00**	0.16	0.27[a]
	Mn	0.09	0.03	-0.19	0.14	-0.05	0.16	**1.00**	-0.01
	Na	-0.08	-0.17	0.53[c]	-0.10	0.08	0.27[a]	-0.01	**1.00**
Female	Br	**1.00**	0.25	0.07	-0.05	0.40[a]	-0.18	0.73[c]	0.18
	Ca	0.25	**1.00**	-0.6	0.13	0.13	0.02	0.34	-0.18
	Cl	0.07	-0.66[c]	**1.00**	0.16	-0.37	0.56[b]	-0.21	0.39[a]
	I	-0.05	0.13	0.16	**1.00**	-0.32	0.19	-0.09	0.45[a]
	K	0.40[a]	0.13	-0.37	-0.32	**1.00**	0.77[c]	-0.19	-0.15
	Mg	-0.18	0.021	0.56b	0.19	0.77[c]	**1.00**	-0.27	0.31
	Mn	0.73[c]	0.341	-0.21	-0.09	-0.19	-0.27	**1.00**	-0.41[a]
	Na	0.18	-0.18	0.39[a]	0.45a	-0.15	0.31	0.41[a]	**1.00**

Statistically significant values: [a] p≤0.05, [b] p≤0.01, [c] p≤0.001.

Discussion

Precision and accuracy of results

Good agreement of the Br, Ca, Cl, I, K, Mg, Mn, and Na contents analyzed by INAA-SLR with the certified data of CRM IAEA H-4 (Table 1) indicates an acceptable accuracy of the results obtained in the study of ChE of the thyroid samples presented in Tables 2-7. The mean values and all selected statistical parameters were calculated for eight ChE (Br, Ca, Cl, I, K, Mg, Mn, and Na) mass fractions in thyroid of female and male (Table 2).

Comparison with published data

Values obtained for Br, Ca, Cl, I, K, Mg, Mn, and Na contents in the normal human thyroid (Table 3) agree well with median of mean values reported by other researches. Data cited in Table 3 also includes samples obtained from patients who died from different non-endocrine diseases. A number of values for ChE mass fractions were not expressed on a dry mass basis by the authors of the cited references. However, we calculated these values using published data for water (75%) [55] and ash (4.16% on dry mass basis) [56] contents in thyroid of adults. The range of means of Br, Ca, Cl, I, K, Mg, Mn, and Na level reported in the literature for normal human thyroid vary widely (Table 3). This can be explained by a dependence of ChE content on many factors, including the region of the thyroid, from which the sample was taken, age, gender, ethnicity, and mass of the gland. Not all these factors were strictly controlled in cited studies. Another and, in our opinion, leading cause of inter-observer variability can be attributed to the accuracy of the analytical techniques, sample preparation methods, and insufficient quality control of results in these studies.

Gender-related differences

A strongly pronounced difference in Br and Mg mass fractions was observed between female and male thyroid (Table 4). The mean Br mass fraction in female thyroids was 1.6 times higher while the mean of Mg mass fraction was 31% lower than in male thyroids. During the first 40 years of life (Age group 1) the situation with ChE contents in female thyroids was some different than that for older females. In Age group 1 no statistically significant difference between the Br content of female and male thyroids was found, but differences between their Ca and Mg contents were detected (Table 5). In Age group 1 of females with mean age 30.9 years the Ca and Mg thyroid contents were about 30% lower than in thyroid of males from the same age group. For ages over 40 years (Age group 2) a statistically significant difference between the Br content in female and male thyroid was observed, but differences between the Ca content in thyroids of females and males, previously found in the Age group 1, was no longer evident (Table 6). However, in this age group a statistically significant reduced level of Mg mass fraction in female thyroids was observed using the non-parametric Wilcoxon-Mann-Whitney U-test. A significant direct inter-correlation between Ca and Mg, K and Mg, Mg and Na, and also Na and Cl, as well as a inverse correlation Br and Cl and Cl and K mass fractions was seen in male thyroids (Table 7). In female thyroids all correlations between ChE found in male thyroids were not observed, except correlations Na and Cl and K and Mg. However, a few other different correlations were found: a direct correlation, Br and K, Br and Mn, Cl and Mg, I and Na, and an inverse correlation, Ca and Cl and Mn and Na.

Because the prevalence of SCH is 10-15 times greater in women than in men [4,10], we can accept the levels and relationships of ChE mass fraction in male thyroid as more suitable (perhaps optimal) for normal function of the gland. If so, we have to conclude that up to age 40 years there is a significant deficiency of Ca and Mg contents in female thyroid parenchyma. In age over 40 significant deficiency of Mg content in female thyroid persist, while the Ca deficiency disappears and an excess of Br is now seen. Moreover, because inter-correlations of ChE contents reflect their relationships one can deduce that relationships of ChE in female thyroids are certainly less optimal that in males.

a) Bromine: The Br is one of the most abundant and ubiquitous of ChE in the biosphere. Inorganic bromide compounds, especially potassium bromide (KBr), sodium bromide (NaBr), and ammonium bromide (NH_4Br), are frequently used as sedatives in Russia [57]. This may be the reason for elevated levels of Br in female thyroid, because females particularly if aged over 40 years use sedatives more intensively than males. Inorganic bromide exerts therapeutic as well as toxic effects. An enhanced intake of bromide could interfere with the metabolism of iodine at the whole-body level, for both elements have similar chemical properties, and are adjacent halogens. So in the thyroid gland the biological behavior of bromide is similar to that of iodide [58]. Therefore, an excessive Br level in the thyroid of elderly females might inhibit thyroid hormonal synthesis.

b) Calcium: Despite the fact that Ca is the most abundant ChE in a human body its role in thyroid health is poorly understood. However, a significant direct correlation between serum Ca and thyroid stimulating hormone (TSH) level was confirmed by the results of many studies [59-61]. The reduced Ca content in female thyroid parenchyma in comparison with the optimal level characteristic of male thyroid can reflect some deficiency of this element in female body. Thus, a deficiency of Ca inhibits TSH secretion and, as consequence, thyroid function.

c) Magnesium: Current biochemical evidence about the elements required to maintain thyroid function shows that these not only include dietary iodine and selenium (Se) but also Mg, because magnesium-ATP contributes to the active process of iodine uptake [62]. Moreover, Mg deficiency can influence bioavailability and tissue distribution of Se which then appears diminished [63]. Similar Ca, there is a significant direct correlation between serum Mg and TSH level [59]. From these data, one can conclude that Mg is involved in the thyroid function. The reduced Ca content in female thyroid parenchyma in comparison with the optimal level characteristic of male thyroid may reflect some deficiency of this element in female body, while a deficiency of Mg has to associate with hypothyroidism. Each of the ChE is distinct in its primary mode of action. Moreover, there are several forms of synergistic action of the ChE as a part of intracellular metabolism. Thus, in addition to ChE content gender-related differences of relationships between them (inter-correlations) might be also involved in etiology of SCH.

Conclusion

Our data elucidate that there is a statistically significant gender-related difference between ChE levels in thyroid tissue of females and males. The Br mass fraction is higher while the Ca and Mg mass fractions are lower in female thyroids compared with those in male thyroids. Subclinical hypothyroidism is a multietiological and multifactorial complex condition. The complete understanding of the role of inadequate levels of some ChE in thyroid parenchyma in the etiology of SCH requires a global vision of their different mechanisms of action, which is not yet possible with the present state of knowledge. However, from the results of our study it follows that an involvement of inadequate contents of intra-thyroidal Br, Ca and Mg in the etiology of female SCH may be assumed.

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