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The effect of 17 years of increased salt iodization on the prevalence and nature of goiter in Croatian schoolchildren

https://doi.org/10.1515/jpem-2018-0129
Received March 18, 2018; accepted June 18, 2018; previously published online July 28, 2018

Abstract

Background: High goiter prevalence caused by iodine deficiency (medium content 5.6 mg potassium iodide [KI]/kg of salt, median urine iodine concentration [UIC] 68 μg/L) in Croatia was observed in 1991 and 1995 when salt was iodized with 10 mg KI/kg. A new regulation introduced in 1996, specified 25 mg KI/kg of salt resulting in an increase of median UIC to 248 μg/L. Afterwards, goiter prevalence was only assessed in two small studies.
Methods: In this study, we investigated the prevalence and etiology of goiter in 3594 schoolchildren 17 years after an increase in salt iodization in Croatia. Thyroid size was determined by palpation in 1777 girls and 1817 boys aged 10–18 years. In goitrous children, a thyroid ultrasound and thyroid-stimulating hormone, free thyroxine (fT4), free triiodothyronine (fT3), thyroid peroxidase (TPO) and thyroglobulin (TG) antibody measurements were performed.
Results: Goiter was found in 32 children (0.89% vs. 2.8% in 1991, $p < 0.00001$ and 27% in 1995, $p < 0.00001$), simple goiter (SG) in 18/32 (56%) goitrous children vs. 126/152 (82.8%) in 1991 $p < 0.00001$, autoimmune thyroiditis (AT) in 13/32 (40.6%) vs. 19/152 (12.5%) in 1991 $p < 0.0009$, nodules in four: two cysts, toxic adenoma and carcinoma (in 1991 two adenomas and one cyst), Graves' disease was not found (four in 1991). Subclinical hypothyroidism was found in three children. Thyroid disease was diagnosed in four of 32 children before the investigation. Increased iodine supply decreased goiter prevalence and SG/AT ratio in goitrous patients.
Conclusions: As thyroid abnormalities were found in 0.89% of children and some required treatment, thyroid examination is important in apparently healthy children regardless of sufficient iodization.

Keywords: children; iodine supply; thyroid diseases; thyromegaly.

Introduction

Iodine is an essential element in thyroid hormonogenesis, and its adequate intake is critical for the prevention of iodine deficiency disorders. Epidemiological survey conducted after the World War II, demonstrated that in about two out of 17 million persons in the former state of Yugoslavia (which also included Croatia) had endemic goiter. In endemic regions, that were populated by six million inhabitants, there were 20,000 cases of endemic cretinism and 2000–4000 deaf mutes [1]. As a result of this investigation, former Yugoslavia introduced the first regulation on compulsory salt iodization with 10 mg potassium iodide (KI)/kg of salt in 1953. These measures resulted in a 3-fold decrease of goiter prevalence among schoolchildren 10 years after the introduction of iodine prophylaxis. Moreover, endemic cretinism was entirely eradicated [2]. In a survey conducted in 1991, nearly 40 years after the introduction of salt iodization in the district of Sibenik located on the Croatian coast, the goiter prevalence was found to be 2.8% among schoolchildren [3]. Another study carried out in 1995, among schoolchildren from different parts of Croatia discovered a goiter rate of 8–35% (with the highest rates in the continental parts of the country) and median urinary iodine concentration (UIC) of 68 μg/L [4, 5]. This finding led to a revision of salt iodization regulation with an increase from 10 to 25 mg KI/kg of salt in 1996.

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The goal of this study was to establish an insight into the current situation of goiter prevalence and etiology 17 years after the last increase of salt iodization in Croatia. The study included 3594 schoolchildren from the district of Nasice located in the continental part of Croatia.

Materials and methods

This study was conducted in 2013 and included 3594 schoolchildren, who ranged in age from 10 to 18 years. There were 1777 girls (49.5%) and 1817 boys (50.5%). The investigation of goiter prevalence was the main goal of this study and the medical examination of schoolchildren was not a part of regular health monitoring. One experienced investigator (M.V., a pediatric endocrinologist) performed an inspection and neck palpation in the outpatient clinics of local schools in the Nasice district to determine the size of the thyroid gland in all 3594 participants. The size of the thyroid gland was determined according to the World Health Organization criteria [6]. The children diagnosed with goiter were advised to visit the University Hospital Zagreb for further examinations by one senior pediatric endocrinologist (JI), including re-examination by palpation of all these children. The following further studies were performed: thyroid ultrasound examination with Aloca ultrasound scanner equipped with 7.5 MHz linear transducer probe and plasma measurement of thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), anti-peroxidase antibodies (TPO ab) and anti-thyroglobulin antibodies (TGA ab) performed using standard biochemical methods.

Criteria for the diagnosis of autoimmune thyroiditis (AT) were increased titer of TPO ab (>100 IU/mL) and/or TGA ab (>100 IU/mL) and heterogeneous and hypoechoic parenchymal echo pattern.

Furthermore, a thyroid scan using Tc-99m was performed in two participants and a percutaneous fine needle aspiration of the thyroid in one participant.

The study protocol was approved by the Ethics Committee of the General Hospital Nasice, and informed consent was obtained from parents or guardians of children with goiter.

Statistical analyses included calculation of percentages and a chi-square (χ^2) test for frequencies between the groups. All analyses were performed using a standard statistical package.

Results

Overall goiter prevalence

Among the 3594 children examined, goiter was detected in 32 (0.89%). In girls, goiter was found in 28 out of 1777 (1.58%), while four out of 1817 (0.22%) boys had goiter, with a male to female ratio of 1:7 (Table 1). According to the first investigator (MV) in Nasice, thyroid enlargement was classified as grade 1 in 30 (94%), grade 2 in two (6%) patients, and that assessment was entirely confirmed by a second investigator in Zagreb.

Simple goiter

Simple goiter (SG) was found in in 18/32 (56%) goitrous patients (15 girls and three boys). All children were euthyroid and had no personal history of goitrogen ingestion. In two girls, the goiter was detected before the study was started (Table 2).

Autoimmune thyroiditis

AT was found in 13/32 (40.6%) goitrous patients with a male:female ratio of 1:12. The clinical and laboratory data of 13 patients with AT are shown in Table 3. In two patients (nos. 1 and 2) AT, as well as hypothyroidism in patients no. 1 were diagnosed before this survey was conducted. The goitrous enlargement was grade 1 in 11, and grade 2 in two patients. In three patients, both TPO ab and TGA ab titre were increased, and in other five patients either TPO ab or TGA ab titer was increased. In one patient, TGA ab were not measured. AT was confirmed by ultrasound in all 13 patients.

Table 1: Prevalence of goiter in 3594 schoolchildren by age and gender.

Age, years	Number of subjects			Number of subjects with goiter, %		
	Girls	Boys	Both	Girls	Boys	Both
10–10.9	234	228	462	4 (1.71)	/	4 (0.87)
11–11.9	252	236	488	2 (0.79)	1 (0.42)	3 (0.61)
12–12.9	224	249	473	2 (0.89)	1 (0.40)	3 (0.63)
13–13.9	254	245	499	6 (2.36)	1 (0.41)	7 (1.40)
14–14.9	243	239	482	5 (2.06)	1 (0.42)	6 (1.24)
15–15.9	190	240	430	4 (2.11)	/	4 (0.93)
16–16.9	210	221	431	3 (1.43)	/	3 (0.70)
17–17.9	170	159	329	2 (1.18)	/	2 (0.61)
Total	1777	1817	3594	28 (1.58)	4 (0.22)	32 (0.89)

Data are presented as number of participants and goiter cases with percentages in parentheses.

In 10 out of 13 patients (nos. 2–10 and no. 13) with AT, the concentrations of TSH, fT4 and fT3 were within normal values. Therapy with L-thyroxine was started in patients nos. 11 and 12 with subclinical hypothyroidism, and reintroduced in patient no. 1 who stopped previously prescribed therapy due to subclinical hypothyroidism.

Nodular lesions

Nodular lesions were found in four children. Only in one 12-year-old girl (Table 2) was the nodule detected by palpation. By ultrasound examination, this nodule was hypoechoic, described as "warm" on scintigraphy with Tc-99m. The plasma level of TSH was suppressed (0.01 mIU/L), fT3 mildly increased (7.1 pmol/L) and fT4 high normal (21 pmol/L). She showed no clear clinical signs of hyperthyroidism except tachycardia. Surgical excision of the nodule was performed and diagnosis of toxic adenoma was confirmed. In one girl and one boy with SG, the thyroid ultrasound detected small cysts (up to 3 mm at the greatest diameter). Moreover, in one girl with AT (Table 3, patient no. 13) the thyroid ultrasound revealed a hypoechoic nodule (7 mm × 4 mm × 6 mm) with microcalcifications. A fine-needle aspiration cytology revealed papillary carcinoma. A total thyroidectomy with central compartment lymph node dissection was performed and histological diagnosis of unifocal papillary carcinoma with no extrathyroid expansion was confirmed. She was treated postoperatively with radioiodine therapy, and therapy with L-thyroxine was introduced. Serum thyroglobulin 3 years after a total thyroid removal remains undetectable.

Table 2: Prevalence of thyroid diseases in 3594 schoolchildren included in the study.

Disease	Number of subjects (%)		
	Girls 1777	Boys 1817	Both 3594
Simple goiter	15 (0.84)	3 (0.16)	18 (0.50)
Cysts[a]	1 (0.05)	1 (0.05)	2 (0.05)
Autoimmune thyroiditis	12 (0.67)	1 (0.05)	13 (0.36)
Papillary carcinoma[b]	1 (0.05)	/	1 (0.02)
Toxic adenoma	1 (0.05)	/	1 (0.02)

Data are presented as number of cases and percentages in parentheses. [a]Discovered by ultrasound in patients with simple goiter. [b]Discovered by ultrasound in a patient with autoimmune thyroiditis.

Prevalence and etiology of goiter in our study in comparison to the results of previously conducted studies

Differences in prevalence and nature of goiter in this study were compared with two previous studies in 1991 [3] and 1995 [4] by a χ^2 test (Table 4). The overall prevalence of goiter discovered by palpation in this study was significantly lower ($p < 0.00001$) than in both of the previous studies [3, 4]. Regarding the etiology of palpable goiter in this study the relative share of SG is significantly lower and of AT is higher in comparison with the Sibenik survey ($p < 0.0001$ and $p = 0.0009$, respectively) (Table 4).

Table 3: Data for clinical examination and laboratory tests in 13 patients with autoimmune thyroiditis at the time of investigation.

Patient number	Age, years	Sex, F/M	Goiter grade	TSH, mIU/L (0.46–4.6)	FT4, pmol/L (10–22)	FT3, pmol/L (1.9–5.7)	TPOAt, IU/mL (<100)	TgAt, IU/mL (<100)
1	15	M	I	11.0	10.8	3.3	1450	71
2	12	F	I	1.1	11.6	3.9	25	1124
3	14	F	I	2.1	12.2	3.4	>3000	96.2
4	15	F	I	2.8	11.1	2.1	>1900	56.6
5	15	F	I	3.5	11.8	3.5	436	353
6	17	F	I	2.1	11.1	2.7	44	145
7	15	F	I	1.8	14.5	5.3	1410	/
8	11	F	I	1.49	14.9	3.29	93	304
9	14	F	I	3.6	11.8	6.6	936	179
10	11	F	I	4.4	13.7	5.6	55	394
11	11	F	II	6.39	11.8	3.1	>7500	917
12	11	F	II	9.55	10.8	4.2	33	1506
13	16	F	I	1.5	10.1	3.7	367	44

Units are indicated and reference ranges for laboratory tests are in parentheses. TSH, thyrotropin; FT4, free thyroxine; FT3, free triiodothyronine.

Table 4: Comparison of prevalence and nature of goiter in studies conducted 1991 in the coastal district Sibenik and 1995 in the continental Slavonia region (before increase in salt iodization), with study conducted 2013 in the continental district Nasice in Slavonia region (after increase in salt iodization).

	Study			Comparison	
District, region	Sibenik (coastal district)	Slavonia (continental region)	Nasice (continental district, Slavonia)	Sibenik vs. Nasice	Slavonia vs. Nasice
Year of investigation	1991	1995	2013		
Reference	Jaksic et al. [3]	Kusic et al. [4]			
Number of schoolchildren in study	n = 5462	n = 245	n = 3594		
Salt iodization	10 mg KI/kg of salt	10 mg KI/kg of salt	25 mg KI/kg of salt		
Goiter	152 (2.8%)	68 (28%)	32 (0.89%)	$p < 0.00001$	$p < 0.00001$
Simple goiter	126/152 (82.8%)	–	18/32 (56.2%)	$p < 0.00001$	–
Autoimmune thyroiditis	19/152 (12.5%)	–	13/32 (40.6%)	$p = 0.0009$	–

Discussion

A high prevalence of goiter among schoolchildren was frequently reported in the 1980s by pediatricians and specialists in school medicine, particularly in the continental parts of Croatia. The first study to determine the actual prevalence and nature of goiter during mandatory iodine supplementation with 10 mg KI/kg of salt was carried out in 1991 on 5462 schoolchildren aged 11–18 years in the coastal district of Sibenik. In this study, goiter prevalence established by palpation was 2.8% (152/5462). SG was found in 126/152 (82.8%) and AT in 19/152 (12.5%) of goitrous patients [3]. A second study, initiated by the Ministry of Health in Croatia, was conducted in 1995 in different parts of Croatia. This study found the prevalence of goiter, assessed by palpation in 2856 schoolchildren aged 7–15 years, to be 8–35%. The lowest prevalence was observed in the coastal regions of the country, while in the northern continental region of Slavonia, where the city of Nasice is located, the prevalence estimated in 245 schoolchildren was 27%. It should be emphasized that in this study only the prevalence but not the etiology of goiter and thyroid function was investigated [4].

Because iodine deficiency was suspected as the primary cause of high prevalence of goiter, the iodine content in salt was measured in 1995 and an insufficient median content of 5.6 mg KI/kg of salt was established. It was also observed that the population with the lowest income used a low-cost, not regularly iodized salt for animal use. Additionally, the food industry also often obtained the salt from the same source. All of these factors contributed to insufficient iodine resulting in an increased goiter prevalence [7]. This was further confirmed by the measurement of UIC: the median UIC in schoolchildren from different parts of Croatia was 68 μg/L (range, 43–90 μg/L) [4, 5]. Evidence of iodine deficiency and its consequences on goiter morbidity in the population changed the mandatory regulation of salt iodization from 10 to 25 mg KI/kg of salt for both human and animal consumption in 1996.

The production and iodization of salt in Croatia is under state supervision and control. Monitoring of salt produced in Croatian plants in 1999, confirmed that all samples contained equal or higher than 20 mg KI/kg salt as a result of the new regulation. Samples of imported salt that supplied a smaller part of the market, revealed that in 15.7% of the salt samples the KI content was below the recommended levels [8].

Following the change in the salt iodization policy in 1996, goiter prevalence (but not the nature of it) was determined in two small studies. The first study was conducted in 2001, comprising 378 schoolchildren in an endemic goiter region of Grobnik (in the north-west continental part of Croatia) and demonstrated a goiter prevalence of 6% [9]. This was significantly lower in comparison to the 61% found in 1961 in the same region [10]. In these two studies, goiter prevalence was determined by palpation and there is no data on the UIC. In the second study conducted in 2009, in the Croatian capital of Zagreb which is located in the central continental part of the country, the thyroid volume was measured by ultrasound in 101 schoolchildren 6–10 years of age. The findings were within the normal range in all participants and the median UIC was 288 μg/L [11]. At the same time, the median UIC measured in 386 schoolchildren, aged 6–10 years from different parts of Croatia, was 241 μg/L (range, 195–288 μg/L), and the authors concluded that iodine sufficiency had been reached in the population (goiter prevalence was not investigated) [11].

Our investigation conducted in 3594 schoolchildren from the Nasice district confirmed that the increase in salt iodization in Croatia resulted in a low goiter prevalence of 0.98%. This is in accordance with the results of other studies which demonstrated that the change from mildly

deficient to sufficient iodine supply was associated with a marked decrease in the prevalence of goiter estimated by palpation or ultrasound examination [12–15].

Nevertheless, some beneficial effects of other factors, besides increased salt iodization, which contributed to observed lower goiter rate, cannot be ruled out in this study. Thus, improved economic conditions resulted in certain changes in the nutrition of the population (consumption of more milk, dairy products and fish), as well as the elimination of non-iodized salt. Additionally, the use of "alternative-source" rock salts (e.g. red, pink, black, Himalayan) lost popularity after repeated warnings of health authorities through various media that these salts are iodine-deficient and thus a health hazard.

Higher prevalence of goiter in girls than in boys in our study corresponds to the results from other investigations carried out in the regions with a normal iodine intake, but we found no change in prevalence with age [3, 15, 16].

We demonstrated that the increase in salt supplementation also resulted in significant changes in the etiology of palpable goiter in our study in comparison to the Sibenik survey [3], conducted before the increase in salt iodization (the modes of diagnostic proceedings in these two studies were the same). The relative share of SG in patients with thyromegaly in our study is lower, and AT higher in comparison with the Sibenik study [3] ($p < 0.0001$ and $p = 0.0009$, respectively) (Table 4), resulting in a decrease in the SG/AT ratio from 6.8/1 in the Sibenik study [3] to 1.4/1 in this study.

In contrast to the Sibenik study, in which four patients with Graves' disease were found in a population of 5462 schoolchildren [3], in this study, there were no cases of Graves' disease among 3594 schoolchildren. Some authors reported increased prevalence of Graves' disease as a result of an increase in iodine intake [17], but as Graves' disease is uncommon in children, our investigated cohort of schoolchildren is small for a valid conclusion.

Although thyroid nodules are uncommon in childhood and adolescence, they require careful consideration because they can be malignant [18]. Only a few studies have estimated their prevalence in the general population of children, but the prevalence depends considerably on the method of detection and on the population evaluated (female gender, increasing age, iodine deficiency and previous radiation exposure, all increase the risk of thyroid nodules). Rallison et al. conducted a survey on 5179 schoolchildren in Utah and Nevada (states exposed to radioactive fallout) as well as in Arizona (using palpation as a screening method), and found 26 benign nodules and two malignant neoplasms [19]. Using the same method, in the general population of Michigan, Matovinovic et al., found exclusively benign nodules in 41/8141 adult participants (none were under 19 years of age) [20]. Furthermore, in the Sibenik study, nodular lesions were found in three of 5462 investigated children (two benign adenomas and one cyst) [3]. In our study, nodular lesions were detected in four of 3594 children (two thyroid cysts, one toxic adenoma and one papillary carcinoma). Only one nodular lesion, later diagnosed as toxic adenoma was detected by palpation. However, cysts and papillary carcinoma were detected by ultrasound examination of the thyroid performed after goiter was discovered by palpation. Before the time of our investigation, thyroid diseases were diagnosed in only two children with SG, two with AT and none with a nodular lesion.

As thyroid size and nodular lesions in our and previous studies conducted in Croatia were assessed by palpation and ultrasound and thyroid antibodies were measured only in children with established thyromegaly, we are aware that true prevalence of goiter, AT and nodules in this study on schoolchildren is probably underestimated.

In conclusion, in comparison with surveys conducted before increased salt iodization, the prevalence of goiter is decreased due to a smaller relative share of SG as a cause of thyromegaly in schoolchildren. As 0.89% of the children in this study had thyroid abnormalities and some of them required treatment, it is of the utmost importance to conduct a careful thyroid examination even in apparently healthy children in regions with adequate iodine supply.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: 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 comparable ethical standards. The study was approved by the Ethics Committee of General Hospital Nasice.

Informed consent: Informed consent was obtained from parents or guardians of children with goiter.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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