ORIGINAL ARTICLE

Assessment of the relationship between urinary iodine level and thyroid dysfunction among children in South India- A case-control study

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Abstract

Background: A universal salt iodization program was implemented in India to eradicate Iodine Deficiency Disorders (IDD) in children. Iodine deficiency is eliminated but excess iodine in children could lead to complications in the thyroid gland. *Aim and Objectives:* To assess urinary iodine levels and thyroid dysfunction among children. *Material and Methods:* One hundred children between the ages of 6 to 12 years with thyroid dysfunctions and 100 age- and gender-matched healthy children were enrolled in the case-control groups respectively. All subjects were measured for urinary iodine, thyroid profile, anti-microsomal antibody, and anti-thyroglobulin antibody levels. Goiter grading and Fine Needle Aspiration Cytology (FNAC) were performed. *Results:* Elevated levels of urinary iodine were found in 77% of the case population. Hypothyroidism (66%), hyperthyroidism (11%), and benign goiter (23%) thyroid complications were observed in the case group. FNAC and autoantibody reports confirmed 66% of autoimmune thyroiditis found in the case group. *Conclusion:* Higher levels of urinary iodine excretion suggest the consumption of excess iodine intake in children. An elevated level of autoantibodies with iodine excess may lead to thyroid complications such as thyroiditis, thyrotoxicosis, and benign goiter in children. So, a continuous supply of iodized salt should be monitored carefully.

Keywords: Universal Salt Iodization, Iodine Excess, Anti-Microsomal Antibody, Urinary Iodine Excretion, Thyrotoxicosis

Introduction

Iodine is a micronutrient required for the production of thyroid hormones and essential for the normal functioning of various organs including the thyroid and mammary gland. It is also important for fetal and infant neurological growth [1]. Lack of iodine leads to Iodine Deficiency Disorders (IDD), which affects all age groups and this is a major public health problem worldwide. IDD comprises a spectrum of diseases which includes goiter, hypothyroidism, cretinism, impaired growth, hearing loss, stillbirths, miscarriage, learning deficits, and brain damage [2]. It is estimated that 2 billion people from 130 developing countries are at risk of developing iodine deficiency [3]. The recommended daily dietary intake of iodine varies from 90 μg/day in

children aged below 6 years, 120 μg/day in children aged 6-12 years, 150 μg/day in adults, and 250 μg/day during pregnancy and lactation [4].

Iodine supplementation was introduced worldwide to prevent iodine deficiency through Universal Salt Iodization (USI). Measuring Urinary Iodine Excretion (UIE) is the best method for assessing iodine dietary intake recommended by World Health Organization (WHO). This index helps evaluate the degree of iodine deficiency and its improvement. The USI implementation has shown impressive progress in eliminating iodine deficiency in the last few decades [5]. Iodine deficiency has been eliminated in goiter endemic areas however, the prevalence of iodine excess and its complications has increased steadily in many countries over the past few years [6-7].

Iodine excess intake shows an association with the formation of thyroid-related disorders, such as Autoimmune Thyroiditis (AT), thyrotoxicosis, and benign goiter [8]. Post-iodination studies observed that Juvenile Autoimmune Thyroiditis (JAT) in the pediatric population has increased [9]. The AT prevalence has increased in areas where people consume excess iodine-rich food in their diet [10]. A few reports have been published in the Indian region, regarding the impact of excessive iodine on thyroid-related disorders in pediatric populations [11-12]. Since diversity in food habits is present in the south Indian population, we decided to conduct this study to find the relationship between urinary iodine levels and thyroid dysfunction among children in our study population.

Material and Methods

Ours was a case-control study in which children aged between 6 to 12 years with thyroid dysfunctions such as hypothyroidism, hyperthyroidism, and goitrous enlargement of the thyroid gland were enrolled in the case group. Children with congenital hypothyroidism, consuming iodine-containing medications, and other endocrine disorders were excluded. Age- and gender-matched healthy children were included in the control group (n=100 children). Purposive sampling (hospital-based) method was used with a random sampling technique for recruiting subjects. UIE, thyroid hormone status, and thyroid auto antibodies of both groups were analyzed. Our study was approved by the Institutional Ethics Committee, Madras Medical College and Rajiv Gandhi Government General Hospital (K.Dis.No. 006859/P&D3/Ethics/Dean/GGH/09), Chennai, Tamilnadu, India. The samples were collected in the Pediatric Endocrinology Unit, Institute of Child Health and Hospital, Madras Medical College, Chennai, Tamilnadu, India.

The sample size was calculated based on a previous article [13], as per below mentioned formula:

$\alpha = 0.05$ (two-sided); $\beta = 0.080$

$n = \{Z1\text{-}a/2 + Z1\text{-}8/2\}^2 \times [P1\ (1\text{-}P1) + P2\ (1\text{-}P2)]/(P1\text{-}\ P2)^2$

$n = \{1.96 + 0.84\}^2 \times [0.535\ (1\text{-}0.48) + 0.34\ (1\text{-}0.34)]/(0.535\text{-}0.34)^2 = 100$

Collection and analysis of blood samples

Five ml blood withdrawn from the peripheral veins of all selected children were transferred into a plain tube, and centrifuged at 3000 rpm for 10 min to separate serum. The collected blood samples were used for measurement of thyroid function test: thyroid stimulating hormone (TSH) [reference range: 0.35-5.0 μIU/ml], free thyroxin (FT4) [reference range: 0.8-2.0 ng/dl], and free triiodothyronine (FT3) [reference range: 2.0-4.4 pg/dl] by ELISA method. The Antimicrobial Antibody (AMA) or thyroperoxidase antibody [reference

range <35 IU/ml] and anti-thyroglobulin antibody (ATG) [reference range: <110 IU/ml] were measured using ELISA method. Five mL of urine was collected from all recruited children to analyze UIE [reference range: 100-200 µg/L] by the Sandell-Kolthoff method [14].

Goiter screening was done by palpation method and goiter was graded based on WHO guidelines [15]. The grades are Grade 0 for no palpable or visible goiter; Grade 1 for goiter is palpable but not visible at the neck normal position and Grade 2 for visible goiter in the neck normal position. The Fine-Needle Aspiration Cytology (FNAC) analysis was performed for goiter in children.

Statistical analysis

The statistical analysis was done by STATA 13 version software. The continuous variables were expressed as mean and Standard Deviation (SD) in the case and control groups. The two group differences were measured using the student's t-test and Mann-Whitney U-test performed for quantitative data. The categorical data has been expressed as frequency and percentages. Chi-square test was performed for qualitative data.

Results

The study consisted of 100 children each in case and control groups. The mean age of case group was 9.02 ± 1.98 years while the control group was 10.12 ± 0.78 years. The mean UIE in case group was 277.20 ± 99.15 µg/L while the control group was 155.82 ±72.55 µg/L (Table 1). There was a significant statistical difference in mean UIE between cases and controls ($p < 0.001$). The results showed excess UIE in cases while control groups showed normal iodine excretion indicating no iodine deficiency.

Table 1: Thyroid hormone profile for case and control groups

Variable	Case group (N=100)	Control group (N=100)	*p*
Age (years)	9.02±1.98	10.12 ± 0.78	0.34
UIE (µg/L) [Ref (100-200)]	277.2± 99.15	155.82 ±72.55	<0.001**
TSH (µIU/ml) [Ref(0.35-5.0)]	17.0± 23.09	2.82 ± 1.56	<0.001**
Ft4 (ng/dl) [Ref(0.8-2.0)]	1.25± 0.90	1.68 ± 0.84	0.0006*
FT3 (pg/dl) [Ref (2.0-4.4)]	2.79 ±1.88	3.27± 1.16	0.0118*
AMA (IU/ml) [Ref (<35)]	66.81±43.95	24.25 ± 19.94	<0.001**
ATG (IU/ml) [Ref. (<110)]	195.56±66.83	42.68±30.21	<0.001**

UIE - Urinary iodine excretion level, TSH - Thyroid-stimulating hormone, FT4 - Free thyroxine, FT3 - free triiodothyronine, AMA – anti-microsomal antibody or anti-thyroperoxidase antibody ATG – anti-Thyroglobulin antibody.
*Value of p *<0.5, **<0.01 indicates statistical significance*

The basic and clinical descriptions of the case population are given in Table 2. The prevalence of goiter was higher in females (66%) and goiter was seen more in the 9-12 years age group of patients. In the case group, based on AMA and FNAC, autoimmune thyroiditis was confirmed in 66% of children and excessive colloid accumulation was present in 34% of children. Goiter grading was carried out among the case population based on WHO criteria and it was found that 6% belonged to Grade 0 - no goiter condition, 28% to Grade 1 goiter, and 66% to Grade 2 goiter (Table 2)

Table 2: The baseline demographic description of the case population

Baseline Profile	**Baseline**	
	n=100	**Percentage (%)**
Gender		
Male	34	34
Female	66	66
Age group		
6-9	22	22
9-12	78	78
Age in years (Mean ± SD)	(9.22 ± 2.04)	
Clinical description of case population		
Percentage of thyroiditis		
Thyroiditis positive (anti-thyroid antibodies)	66	66
Thyroiditis negative	34	34
Fine-needle aspiration cytology		
Colloid	34	38
Thyroiditis	66	60
Ultrasonography		
Thyroiditis	66	56
Thyromegaly	34	41
Goiter Grading		
0	6	6
1	28	28
2	66	66

The iodine nutritional status of children was calculated by measuring UIE and classified based on WHO criteria (Table 3). The excretory iodine level was found to be more than adequate in 77% children and among them excessive iodine excretion was seen in 50% (>300 µg/L of UIE), while 18% had normal iodine status and 5% showed less than the normal excretory level of iodine (Table 3, Figure 1).

Based on the thyroid hormone profile, FNAC report, and antibody titters, the 100 pediatric patients were classified into three groups. Group I included thyroiditis patients (n=66), and the mean UIE value was 285.44 µg/L. Group II included thyrotoxicosis patients (n=11), and the mean UIE value was 301.36 µg/L. Group III included benign goiter patients (n=23) and mean UIE values was 255.15 µg/L (Table 4). Excess urinary iodine excretion was found in all three groups.

Table 3: Iodine nutrition status based on urinary iodine excretion

Mean UIE	N	Iodine nutrition status
<100	5	Iodine deficiency
100 – 199	18	Adequate iodine nutrition
200 – 299	27	More than adequate iodine nutrition
300 +	50	Excessive Iodine nutrition

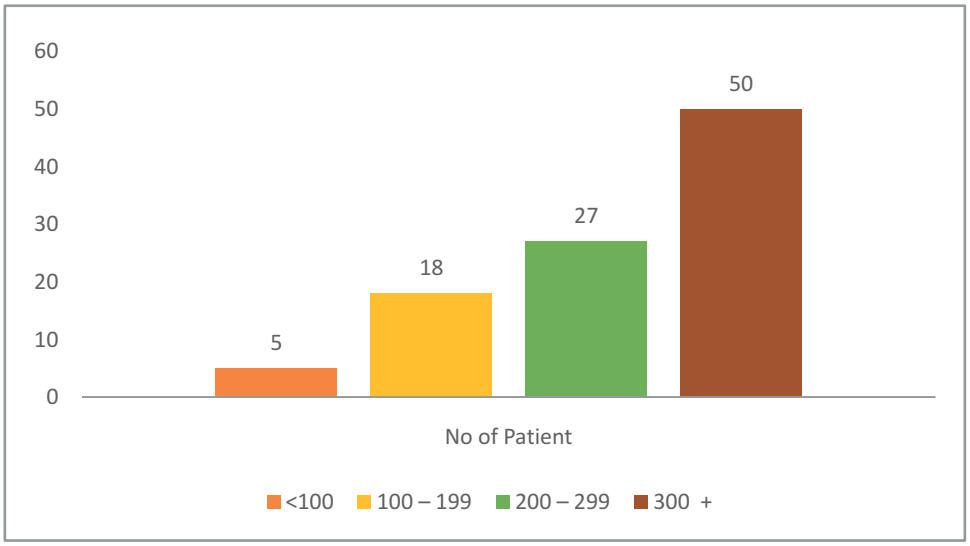

Figure 1: Iodine nutrition status based on urinary iodine excretion

Table 4: Classification based on thyroid complication

Group	Disorder	N	Mean UIE (µg/L)
Group I	Thyroiditis	66	285.44
Group II	Thyrotoxicosis	11	301.36
Group III	Benign goitre	23	255.15

Group I (Thyroiditis)

In this group, the mean value of UIE was 285.44 µg//L. This was above the median value of iodine excretion 100-200 µg/L. Based on the thyroid hormone profile, this group was subdivided into three groups (Table 5). All three sub-groups had above the median excretion iodine value.

Group II (Thyrotoxicosis)

In this group, the mean UIE was 301.36 µg/L, TSH 0.013 µIU/ml, FT4 was 3.5 ng/dl, FT3 7.08 pg/ml and AMA 112.10 IU/ml and ATG 306.09 IU/ml. In this group too, UIE was above the median excretion iodine value.

Group III (Benign goiter)

In this group, the mean UIE was 255.15 µg/L. Based on the thyroid hormone profile this group was divided into two sub-groups (Table 6). The UIE values were maximum in the hypothyroid group.

Table 5: Thyroiditis group

Physiological State	N	UIE (µg/L)	TSH (µIU/ml)	FT4 (ng/dl)	FT3 (pg/dl)	AMA (IU/ml)	ATG (IU/ml)
Hypothyroid	42	288.45	32.37	0.84	1.76	63.53	204.41
Hyperthyroid	08	307.5	0.0125	3.71	6.87	97.02	317
Euthyroid	16	265.63	2.64	1.18	3.22	66.19	143.87

Table 6: Benign goiter group

Physiological state	N	UIE (µg/L)	TSH (µIU/ml)	FT4 (ng/dl)	FT3 (pg/dl)	AMA (IU/ml)	ATG (IU/ml)
Euthyroid	17	245.29	4.26	1.16	2.99	50.84	152.23
Hypothyroid	06	267.5	9.93	1.06	2.75	63.48	186.9

Discussion

Iodine deficiency in India was eradicated by iodine supplementation which was introduced in 1992 as National Goiter Control Program which was later changed to prevention of IDD [16]. The state of Tamilnadu in South India has been focusing more on the eradication of IDD among children through salt iodization for the last three decades. Even though iodine deficiency has been eliminated, goiter is still prevalent in India. The post-iodization assessment study of South Asian countries reported an increased prevalence of JAT in children in these countries [12, 17]. Post-iodination studies in India reported that the prevalence of goiter was 13%, subclinical hypothyroidism was 10%, and childhood hypothyroidism was 3% [18]. This study was designed based on the available knowledge, to assess the iodine nutritional status of thyromegaly in school children from South India.

In this study, we observed in the case group that two-thirds had thyroiditis, one-third had benign goiters, and the remaining exhibited thyrotoxicosis. All groups showed above median urinary iodine excretion value (100-200 μg/L), indicating no dietary iodine deficiency. When the case group was compared with the control group, the results showed an excess excretion of urinary iodine in cases indicating an excess amount of iodine intake, which may be causing deranged metabolism in the thyroid gland. The UIE was maximum in patients with thyrotoxicosis and thyroiditis, followed by benign goiter in pediatric patients. We also observed that thyroiditis was 66%, benign goiter 23%, and thyrotoxicosis 11% in the case group.

Increased iodine excretion in urine was a common hallmark among all these pediatric patients with thyroid disorders.

Our study observation is similar to the previous studies stating the elimination of iodine deficiency but increased autoimmune thyroiditis [19-21] and residual goiter in children [6]. High iodine intake could trigger autoimmune thyroiditis in hypothyroidism patients [22]. Findings in our study are similar to other studies from Tamilnadu, [11, 13] Western India, [12] and Western countries which reported that higher values of UIE was present maximum in autoimmune thyroiditis patients in children [23-25]. Children who had elevated levels of two types of anti-thyroid antibodies were at risk for developing thyroid dysfunction if they consumed more iodine than required [26]. The patients with or with goiter status of hypothyroidism or hyperthyroidism may exhibit differences in the production of auto antibodies production. Children with iodine excess are more likely to develop juvenile thyroiditis that leads to hypothyroidism requiring lifelong thyroxin replacement.

Limitations

This study was a hospital-based study. Detailed community study is required to identify the mechanism behind this scenario along with the associated molecular and environmental factors in a larger sample

Conclusion

Fewer changes were observed in iodine deficiency in coastal areas of south India, like Tamilnadu, after the implementation of the USI programme. This programme has eliminated iodine deficiency in India however it increased iodine excess-related thyroid complications reported in many studies. This suggests any child with thyroid dysfunction requires a complete thyroid checkup before

supplementing iodized salt. Supplementation programs may be tailored to a particular region and monitoring salt iodization program properly is needed to achieve an acceptable iodine status. Unionized salt is needed to be provided in the market to patients with thyroiditis, thyrotoxicosis, and other thyroid complications.

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