

Improving iodine nutritional status and increasing prevalence of autoimmune thyroiditis in children

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ABSTRACT

Objective: The objective of this study is to evaluate the link between excess iodine intake as evidenced by increased urinary iodine excretion (UIE) and autoimmune thyroiditis in children and to assess the correlation between UIE and thyroid microsomal antibody (thyroid peroxidase [TPO]) titers in children. **Materials and Methods:** All children with goiter between age group 6 and 12 years, were subjected to blood tests for free thyroxine, thyroid stimulating hormone, and TPO antibody, fine needle aspiration was advised for all children with goiter. Forty-three children with confirmed autoimmune thyroiditis served as cases, and 43 children with euthyroid goiter with workup negative for autoimmune thyroiditis and iodine deficiency were enrolled as controls. UIE was estimated in spot urine sample for both cases and controls. The levels of urinary iodine were compared between cases and controls. **Results:** The levels of urinary iodine were significantly higher in children with autoimmune thyroiditis as compared with control. There was a positive correlation between UIE and antimicrosomal antibody titers among cases. Among cases 65% children had subclinical hypothyroidism, 27.9% had overt hypothyroidism and 7% of cases, and 100% of controls had euthyroid functional status. Excessive ($\geq 300 \mu\text{g/L}$) UIE was strongly associated with autoimmune thyroiditis. If the UIE level is $\geq 300 \mu\text{g/L}$, then there is 17.94 times higher chance of having amiodarone-induced thyrotoxicosis than those who have UIE level $< 300 \mu\text{g/L}$ ($P < 0.001$). **Conclusions:** A possible association between increased iodine intake and autoimmune thyroiditis was found in this study. Excessive iodine intake may trigger thyroid autoimmunity and eventually thyroid hypofunction.

Key words: Hashimoto, iodine, thyroiditis

INTRODUCTION

Following the implementation of National Iodine Deficiency Disorders Control Programme based on Universal Salt Iodization (USI), there are reports of normalization of iodine nutrition as reflected by urinary iodine excretion (UIE) from the country.^[1,2] According to current recommendations by the World Health

Organization, median urinary iodine concentration of 100–199 $\mu\text{g/L}$ in samples from school children indicate adequate iodine intake and optimal iodine nutrition.^[3] The UIE is the primary indicator for a person's iodine nutritional status and the primary variable used to measure the success of iodine supplementation in a population.^[4]

It is well known that when a cohort is supplemented with iodine, the pattern of thyroid diseases is bound to undergo a definitive change. Many researchers from the western world began to observe an increase in Juvenile autoimmune thyroiditis (JAT) in populations who have

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been supplemented with iodine. Predominant studies in this arena are from the western world and population-based studies. Hence, we decided to perform this study to evaluate the link between excess iodine intake as evidenced by increased UIE and autoimmune thyroiditis in children and correlation between UIE and thyroid microsomal antibody (TMA) (thyroid peroxidase [TPO]) titers in children.

MATERIALS AND METHODS

We conducted this study as a case–control study over a period of 3 years from February 2010 to February 2014. The study was initiated after institutional ethical committee approval. All children aged 6–12 years with goiter attending the pediatric endocrinology outpatient department were evaluated for autoimmune thyroiditis as per standard protocols.^[5] Goiter with autoimmune thyroiditis served as cases. Children with goiter but workup negative for autoimmune thyroiditis and iodine deficiency disorder were considered to be controls (one control per case recruited). Children with proven congenital hypothyroidism, iodine deficiency disorder, other endocrine disorder, and history of taking iodine-containing medications were excluded from the study. Children with goiter were subjected to blood tests for free thyroxine (FT4), thyroid stimulating hormone (TSH) and TPO antibody, fine needle aspiration was advised for all children with goiter. UIE was estimated in spot urine sample for both cases and controls. Definitions used in the study are shown in Table 1.

The stained slides were reported blindly by a cytopathologist, who had no access to clinical and serological data. The criteria adopted for the diagnosis of autoimmune thyroiditis were: the presence of lymphocytic infiltrate, diminished colloid, and minimal to moderate follicular destruction, with or without Hürthle cell change.^[6]

T4 and TSH were estimated by enzyme immunoassay method. The normal range of FT4 as standardized in our laboratory was 7.3–13.4 pM/L and for TSH 0.5–5 μ IU/mL. TMAs were tested by electrochemiluminescence assay (Cobas-Roche- Elecsys1010 analyzer), titers \geq 34 IU/L were considered positive. Spot urine samples were collected in a wide-mouthed plastic container with tight screw tops and kept in a refrigerator at -4° C after addition of 1 drop of toluene. Urine was digested with ammonium persulfate to get rid of interfering substances; then iodide was measured by its catalytic action on the reduction of ceric ammonium sulfate (yellow) to the cerous form (colorless), coupled to oxidation of arsenite to arsenate (Sandell–Kolthoff reaction).^[7]

Statistical analysis

Data were entered using Microsoft corp., Excel and analyzed using SPSS statistics for windows, version 20, Chicago, IL, USA. For continuous data mean with standard deviation and median were calculated. Mann–Whitney U-test was used to compare the difference between median UIE between cases and controls. Correlation between urinary iodine and antimicrosomal antibody (AMA) titers was analyzed by arriving at Pearson correlation coefficient (R value). Logistic regression was used to find the association between excess UIE levels, sex, family history of thyroid disease and autoimmune thyroiditis. All tests are considered statistically significant at $P < 0.01$.

RESULTS

During the study, 91 children presented to the thyroid clinic with goiter. Of these, 4 children with mild iodine deficiency and 1 child with dysmorphogenesis were excluded from this study. Thus, 86 children (43 cases and controls each) satisfied the necessary criteria and were recruited into the study. The baseline demographic, clinical, biochemical parameters of the study population are depicted in Table 2.

Table 1: Study definitions

Study parameter	Definition
JAT	Cytopathological features consistent with lymphocytic thyroiditis or with positive titers of anti-microsomal antibodies
Simple colloid goiter	No clinical or laboratory evidence of thyroid dysfunction with negative antibody titers and cytology is consistent with colloid goiter
Subclinical hypothyroidism	Normal T4 levels and elevated serum TSH levels (>5 μ IU/mL)
Overt hypothyroidism	Low T4 (<7.3 pM/L) and high TSH (>5 μ IU/mL)
UIE (μ g/L) ^[8]	
Excessive	≥ 300
More than optimal	200-299
Optimal	100-199

JAT: Juvenile autoimmune thyroiditis, UIE: Urinary iodine excretion, TSH: Thyroid stimulating hormone, T4: Thyroxine

Table 2: Description of the study population

Variables	Mean \pm SD (n=43)	
	Cases	Control
Age (years)	9.91 \pm 1.26	9.42 \pm 1.60
TSH (μ IU/mL)	24.28 \pm 15.38	3.30 \pm 4.93
FT4 (pM/L)	9.34 \pm 2.16	20.3 \pm 1.32
UIE (μ g/L)	329.53 \pm 80.81	214.30 \pm 78.46
TMA Ab (IU/L)	167.46 \pm 93.17	8.24 \pm 5.35
Thyroid functional status, n (%)		
Overt hypothyroidism	12 (27.9)	0
Subclinical hypothyroidism	28 (65.11)	0
Euthyroidism	3 (6.97)	43 (100)

TSH: Thyroid stimulating hormone, FT4: Free thyroxine, UIE: Urinary iodine excretion, TMA: Thyroid microsomal, Ab: Antibody, SD: Standard deviation

The study population was divided as per the iodine status as adequate, above adequate requirements, and excessive iodine status (median UIE 100–199 µg/L, 200–299 µg/L, and ≥300 µg/L, respectively). 9.3%, 16.3%, and 74.4% of cases fell in the adequate, above adequate, and excessive, respectively. The corresponding percentages in controls were: 62.8%, 23.3%, and 14%, respectively [Figure 1a; $P < 0.05$]. The levels of urinary iodine were significantly higher in children with autoimmune thyroiditis as compared with controls (329.53 ± 80.813 vs. 214.30 ± 78.464 µg/L $P < 0.001$) [Figure 1b].

To elucidate the relationship between UIE and JAT, a correlation analysis was performed between UIE levels and AMA titers. A positive correlation between UIE and AMA titers ($R = 0.503$ and $P < 0.001$) among cases was observed [Figure 2].

The factors associated with JAT: Age, UIE levels, sex, family history of thyroid disease was considered, and their independent influence over JAT analyzed by a logistic regression analysis. It was observed that the odds of having UIE level ≥ 300 µg/L is 17.94 in cases versus controls (odds ratio 17.94, 95% confidence interval 5.96–53.97 $P < 0.001$). None of the study subjects had hyperthyroidism.

DISCUSSION

To the best of our knowledge, this is the first study investigating the impact of excessive iodine on thyroid autoimmunity in a clinic-based setting from South India.

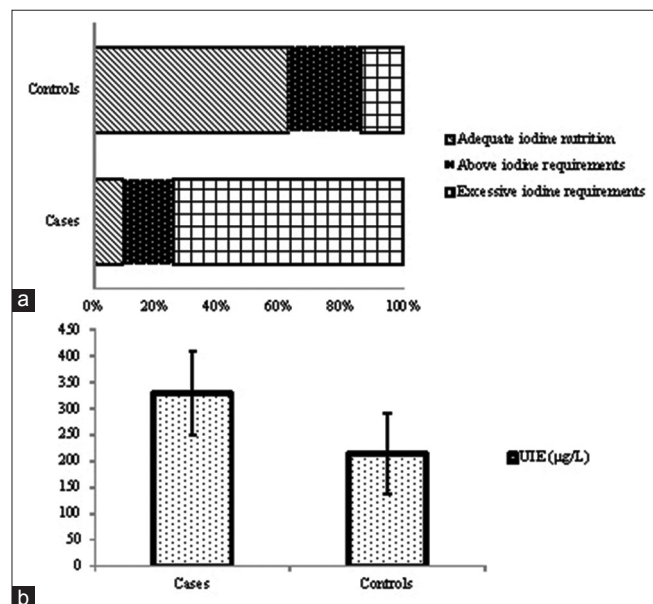


Figure 1: (a) Urinary iodine excretion levels in case and controls as per the World Health Organization definitions. (b) Comparison of mean urinary iodine excretion levels in cases and controls. * $P < 0.05$

We observed 63.9% of the study sample to have higher than optimal UIE. Children with JAT had higher UIE levels. A significant correlation was observed between UIE levels and AMA titers in children with JAT.

In this study, 90.7% ($n = 39$) of the cases and 37.3% ($n = 16$) of the controls exhibited higher than optimal UIE. The high UIE of the present study may reflect a trend with time with improved penetration and execution of USI program. A possibility of nonsalt sources of iodine like domestic water filters, based on polyiodide resin technology can provide 3000–6000 µg of iodine per day to an individual,^[9] that could contribute to high UIE or it can be hypothesized due to the inability of the diseased thyroid to trap available iodine efficiently. This observation is in agreement with Marwaha *et al.*^[10] and Bazrafshan *et al.*^[11] However, one must remember that these were community-based studies and ours in a clinic-based study; hence, the element of referral bias must be taken into account.

The association between increased UIE and JAT has been supported by the previous studies;^[12–15] refuted by Zimmermann, *et al.*^[16] and BacZyk, *et al.*^[17] We observed a significantly higher median Iodine levels in children with JAT versus children without (329.53 ± 80.813 vs. 214.30 ± 78.464 µg/L $P < 0.001$).^[18] This is in line with the study from North India by Gopalakrishnan, *et al.*^[18] (166 µg/L in children with JAT versus 133 µg/L in children without JAT, $P < 0.05$). However, Zois, *et al.* did not observe any difference in Median UIE in children with and without JAT.^[19] The possible explanations attributable to our observation include:

- Iodine toxicity hypothesis – Iodine undergoes peroxidation and generates free radicals and causes thyroid cell destruction^[20,21]
- Increased immunogenicity of the iodinated thyroglobulin^[22]

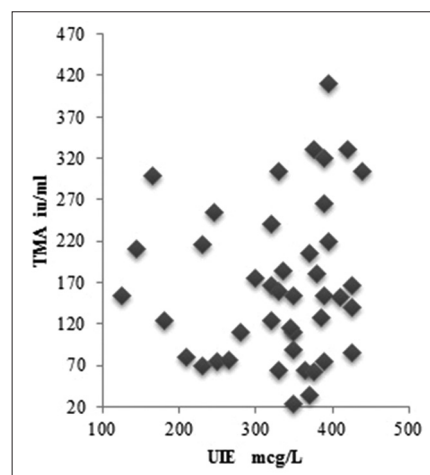


Figure 2: Depiction of correlation between thyroid microsomal antibody levels and urinary iodine excretion levels. $R = 0.503$, $P < 0.05$

- c. Direct stimulation of the immune system by the iodine.^[23]

We observed a weak, but significant correlation between UIE levels and TMA antibody titers ($R = 0.501$). A lack of correlation has been reported from a Srilankan study ($R = 0.44$, $P = 0.3$) and Zois, *et al.*^[19] The biological explanation to this observation would be that Iodine plays a permissive role, not causative role, in the background of genetic predisposition.

Based on logistic regression analysis, we observed that the odds of having UIE level $\geq 300 \mu\text{g/L}$ are 17.94 among children with JAT to those without. This is in agreement with the results of Zois *et al.*^[19] who concluded silent iodine prophylaxis resulted in the elimination of iodine deficiency in Greece, and this has been accompanied by an increase in the prevalence of autoimmune thyroiditis. However, Kaloumenou observed family history, female sex as strong determining factors for the occurrence of JAT, over excessive iodine intake.^[24] It is also interesting to note that none of our subjects developed hyperthyroidism during the study. Iodine-induced hyperthyroidism related to thyroid autonomy has been reported previously.^[25,26] Whether this is related to small sample size or genetic factors that merit further exploration cannot be answered at this point of time.

We wish to clarify certain issues pertaining to the methodology adopted in the study. We applied both serological and cytomorphological criteria to diagnose autoimmune thyroiditis. It is recognized that antibody titers might change, but cytomorphological features persist during the clinical course of amiodarone-induced thyrotoxicosis (AIT) indicating the need to combine cytological and serological evaluation to diagnose AIT.^[27] Furthermore, we have selected only prepubertal subjects for the study purpose to eliminate the immune modulatory effects of pubertal hormones on antibody titers. Previous studies have considered children with negative antibody titers as controls. Considering ethical issues, we included children with simple colloid goiter as controls as an estimation of anti-TMA titers and urine iodine would be a part of the routine evaluation of the condition.

Our study is not without limitations. Ours is a clinic-based study, not a community-based one, which would be ideal. Lack of periodization data does not permit the conclusion that high value of iodine in AIT is due to salt iodization. Salt iodine content was not estimated, and the amount of salt consumption was not quantified in this study.

CONCLUSIONS

We observed a possible association between increased iodine intake and autoimmune thyroiditis. Excessive iodine intake may trigger thyroid autoimmunity and eventually thyroid hypofunction. Proper monitoring of the salt iodization program is essential to achieve acceptable iodine status. If a causal relationship is established by future research, then supplementation programs can be tailored to the need of the particular region.

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Conflicts of interest

There are no conflicts of interest.

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