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ORIGINAL ARTICLE

Clinico-Etiological Profile of Goitrous Children of a Coastal Area and the Association Between Urinary Iodine Concentration and Thyroid Autoimmunity

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Abstract

Background: Iodine deficiency is unlikely to be a main cause of goitre in a coastal area, with a predominant sea food eating population. At the same time, excess iodine may cause thyroid autoimmunity and hypothyroidism via the Wolff-Chaikoff effect. Measurement of Urinary Iodine Concentration (UIC) per day is an excellent substitute for assessing the iodine intake. The objectives of this study are to describe the clinico-etiological profile and to determine the correlation between Urinary Iodine Concentration and thyroid autoimmunity in goitrous children below 12 years of age attending a tertiary care institute in a coastal area. **Materials & Methods:** It was a cross-sectional analytical study in a coastal tertiary care institute. Children attending the department of Pediatrics were screened for goitre. UIC and thyroid autoimmunity were ascertained using standard techniques. **Results:** Nearly 1/3rd of goitrous children had thyroid autoimmunity. The median Urinary Iodine Concentration (UIC) of the study area was 210 µ/L, which is above adequate level, as per WHO grading. **Conclusion:** Thyroid autoimmunity is an important cause for goiter in children from this coastal area and a high iodine intake may be contributing to this. Hence, the salt iodization in coastal areas may need a reconsideration. However, further community-based studies may help to provide an epidemiological level of recommendation regarding the iodine supplementation (salt iodization) in coastal areas.

Keywords: Autoimmune thyroiditis, Excess urinary iodine, Goitre in children, Median Urinary Iodine Concentration, Salt iodisation

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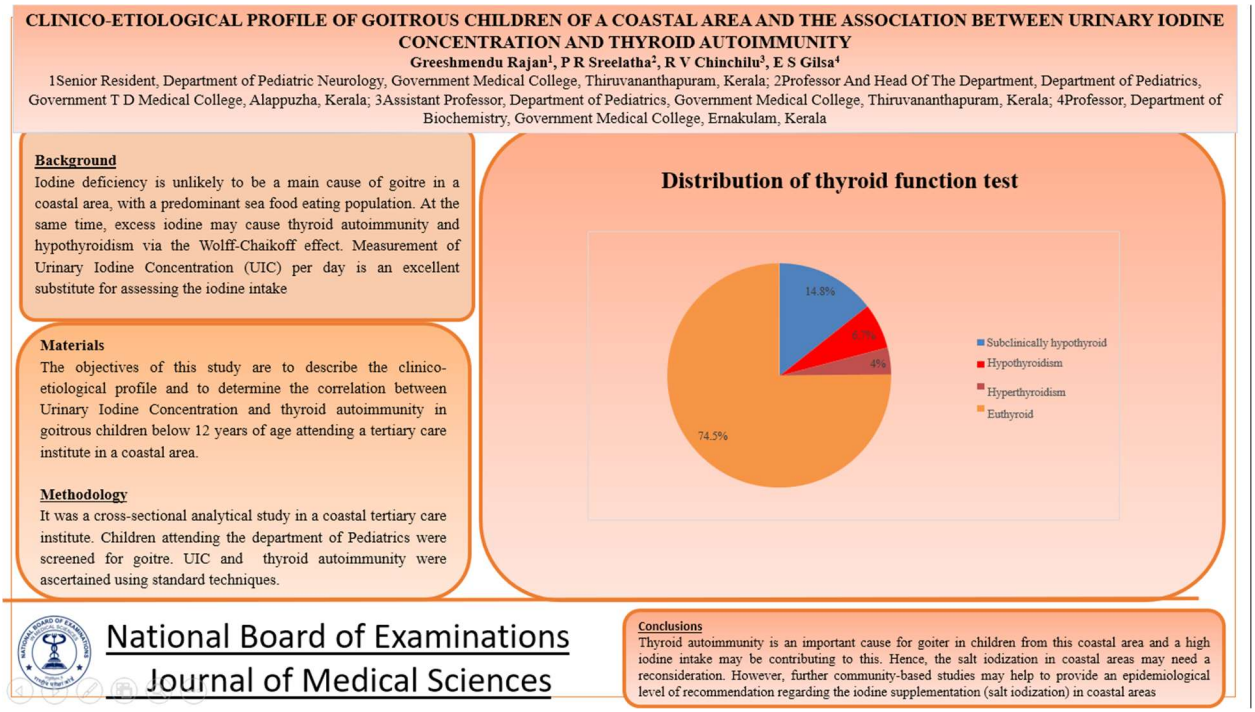
Graphical Abstract



Introduction

One of the most prevalent endocrine conditions affecting children is thyroid dysfunction. Goitre is often seen in children with thyroid disorders. They may have a hyperthyroid, hypothyroid, or euthyroid presentation [1]. Iodine deficiency is the most frequent cause of goitre in children worldwide. However, persistent autoimmune thyroiditis is frequently cited as the most frequent cause of pediatric goitre in regions with adequate iodine intake [2]. Iodine is a necessary micronutrient for healthy human growth and development. According to assessments by the Indian Council of Medical Research and the Directorate General of Health Services, 337 of 414 districts had an endemic status for iodine deficiency disorders, meaning that their frequency was greater than 5%. Aiming to reduce the prevalence of iodine deficiency disorders to less than 5%, the National Iodine Deficiency Disorders Control Programme (NIDDCP), which is being implemented in all States and Union Territories, was started by the Indian government in recognition of the overall seriousness of the situation. [3] A study conducted in Ethiopian school children revealed that the median UIC was 518 micrograms/liter, raising concerns about the potential for excessive iodine intake. According to the study, the prevalence of pediatric goitre has dramatically decreased since nationwide salt iodization was implemented. However, it also considers the possibility that school children may have consumed too much iodine based on their UIC level. [4] Chronic exposure to excessive iodine from water or poorly managed salt is a risk factor for hypothyroidism in free-living people, despite the fact that universal salt iodization has remarkably reduced goitre

rates. To prevent thyroid disorders, it is crucial to keep an eye on the levels of iodine in salt and drinking water [5]. Goitre, hypothyroidism, hyperthyroidism, and/or thyroid autoimmunity can all be brought on by excessive iodine consumption. An increase in iodine consumption, often at intakes only marginally above physiological needs, may make people who already have thyroid illness or have previously been exposed to iodine deficiency more vulnerable to thyroid problems [6].

Numerous research has been carried out to demarcate causes of childhood goitre, and iodine deficiency is a well appreciated etiology of endemic goitre. Investigating the etiology of goitre with highlight on iodine status is pertinent in this context, particularly for schoolchildren in coastal areas, who are less likely to suffer from an iodine deficit due to their diet of predominant seafood. We therefore designed this study with intention to demarcate the profile of goitrous children and to ascertain the relationship between Urinary Iodine Concentration and thyroid autoimmunity along with estimating the median UIC among the school children of a coastal area. This study aims to describe the clinico-etiological profile of goitrous children in a coastal area and evaluate the correlation between urinary iodine concentration and thyroid autoimmunity and thus to assess whether excessive iodine intake contributes to thyroid autoimmunity in this population.

Materials and Methods

It was a cross sectional analytical study conducted among out patients and in patients in the age group of 1 to 12 years attending the Department of Paediatrics, Government TD Medical College Hospital, Alappuzha from December 2018 to November 2019.

Inclusion Criteria

Case definition - Goitre is defined as the condition where there each of the lateral lobe of the thyroid gland is larger than the terminal phalanx of the thumb of the person examined.

The WHO goitre grading system is as follows [7]:

Grade 0	Goitre is not palpable or visible even when the neck is extended
Grade 1	When the goitre is palpable
Grade 1A	Goitre detected on palpation
Grade 1B	Goitre palpable and visible when neck extended
Grade 2	Goitre visible when neck is in the normal position
Grade 3	Large goitre visible from distance

Thus, children, in the age group 1 to 12 years, having goitre equal to or above grade 1b were included in the study.

Exclusion Criteria

Children on thyroxine supplementation or anti thyroid medications.

Sample Size

The sample size was calculated based on a study conducted by Boyages et al, in a study sample of goitrous children. [8] The formula applied is 4pq/d2 Where, P is the prevalence of anti-thyroid antibody positivity, and d is the precision (20 percentage of prevalence). The prevalence of thyroid autoimmunity in the study group was 60 %. A dropout of 10 percentage is expected. The thus calculated sample size is taken to be 74.

Study Procedure

Initially, the medical officers and the residents were sensitised to screen visually for goitre. All the children so detected to have goitre were then evaluated by the principal investigator alone. Children with goitre (grade 1B or above) in the age group of 1 to 12 years were enrolled in the study. The screening was based on visual inspection alone. All details about the study were explained to the subjects and their parents and a written informed consent was obtained from the parent if the child was below 7 years of age, whereas assent was obtained from the child, if the child was above 7 years of age. The clinico-epidemiological profile of children detected with goitre was then ascertained. We used the recall method to delve into the subjects' dietary history, which included the frequency of intake of both goitrogens and foods high in iodine. For ascertaining serum FT4, TSH, serum anti-TPO positivity 5 mL of blood was collected from each child, and was rotated at 5000 rpm for 10 minutes, and serum was separated. The serum samples were stored in deep freezer at -20 degree Celsius, or could also be contained in room temperature if not for more than a period of 24 hours. The parameters were ascertained using Fully Automated Immuno-assay Analyser by Beckman Coulter access 2 (FDA approved chemiluminescence method). The lot number of reagent used was 871023, and batch number was V5P8SPT6J92QK5JJSV. For estimation of urinary iodine, WHO recommended Method A, based on colourimetry using Ammonium persulfate as reagent was employed. Minimum amount of urine needed was 250 microlitre per sample, and the urine samples were also stored in deep freezer at –20 degree Celsius. Ultrasonography of the thyroid gland was done with reference to the gross morphology and echotexture, and was done by a single radiologist using Siemans 2 D Ultrasonography.

Data Analysis

All the data was entered in Microsoft Excel Sheet and analysed using SPSS version 22. Qualitative variables were expressed in percentages and quantitative variables were summarized in mean with standard deviation, and median where necessary. The tests of significance used were unpaired t test for quantitative variables and chi square test for qualitative variables. Pearson’s correlation coefficient was used to ascertain the

association between Urinary Iodine Concentration and anti TPO. A p value of less than 0.05 was considered to be statistically significant

Results

The study included 74 children with goitre, of whom 50 were girls (male: female ratio of 1:2). With a range of 3 to 12 years, the average age at presentation was 9.36 years +/- 2 years. Forty children (54%) were aged more than 10 years. Table 1 shows the distribution of the goitre grade. Thirty-three children (44.6%) in the study sample had a family history of thyroid dysfunction manifested as goitre, or a history of thyroid-related drug use or thyroid surgery. Goitre lasted an average of 5 +/- 7.3 months. It was shown from the diet history that children with higher grades of goitre (grades 2 and 3) consumed more goitrogens and iodine, albeit this difference was not statistically significant. The study sample's mean FT4 value was 0.94 +/- 0.68 ng/dL. The study sample's mean TSH level was 6.7 +/- 20.8 micro-IU/mL. Tables 2, 3, and Figure 1 show the distribution of thyroid function tests. Of the children, 55 (74.5%) were euthyroid. Three children (11%) were biochemically hypothyroid out of the 26 children with a history suggestive of hypothyroidism.

Three children had a history suggestive of hyperthyroidism, among which one child was biochemically hyperthyroid. She complained of having large eyes, tremors, and weight loss. She had tremor and eye signs during evaluation. Her TSH was low and her FT4 had increased. Additionally, she tested positive for anti-TSH and anti-TPO receptor antibodies. Thyroid gland ultrasonography revealed heterogeneous echotexture in 31 children (41.9%), which was suggestive of autoimmune thyroiditis. Nineteen (61%) of these children were anti-TPO positive. Among the five children with hypothyroidism, three children (60%) were having UIC indicative of iodine intake above requirement, and one child (20%) was having anti TPO positivity. Among the 11 children with subclinical hypothyroidism, nine children (82%) were having UIC indicative of iodine intake above requirement, and six children (54.5%) had anti TPO positivity.

Thyroid autoimmunity

Thyroid autoimmunity (anti-TPO positivity) was seen in 27 children (36.5%) in the study sample. Eleven of these children (39.1%) had grade 2 goitre, twelve (4.3%) had grade 3 goitre, and fifteen (56.5%) had grade 1b goitre. Goitre lasted for an average of seven months. Compared to children who were anti-TPO negative, those who were anti-TPO positive consumed more iodine-rich food.

Nine children (33.3%) among the children with thyroid autoimmunity were subclinically hypothyroid. Three children (11%) had a history of hyperthyroidism among which 1 child was biochemically hyperthyroid.

Iodine intake and thyroid autoimmunity

Among the 27 children with anti-TPO positivity, 13 children (48.5%) were having an iodine intake above the requirement. Five children (18.5%) had excessive iodine intake. Nine children (33.3%) had adequate iodine nutrition. This difference was found to be

statistically significant (p<0.0001). The quantitative levels of UIC and anti-TPO were correlated. Pearson's correlation coefficient was 0.496 (p-0.0002). Thus, there was a moderately positive correlation that was statistically significant (Figure 3). Figure 4 illustrates the relationship between thyroid autoimmunity and urinary iodine concentration.

Urinary Iodine Concentration

The median UIC was 210 micrograms/Litre, which as per the WHO implies an iodine intake above the requirement [7]. Urinary iodine concentration in 47 children (63.5%) were higher than 200 micrograms/liter (p-0.01). This indicated that 63.5% of the children were consuming more iodine than was recommended. Figure 2 depicts the distribution of UIC. Thyroid dysfunction was observed to be more common in children whose urine iodine concentration was greater than 200 micrograms/liter than in those whose concentration was less than 200 micrograms/liter (Table 4).

When compared to children with UIC levels below 200 micrograms/liter, children with UIC levels of 200 micrograms/liter or more had a greater percentage of thyroiditis as per USG. Twenty-one children (44.7%) had USG findings of thyroiditis among children with more than adequate iodine intake (UIC >/= 200 micrograms/L), while only ten children (37%) had USG findings of thyroiditis among children with UIC<200 micrograms/L (p>0.05).

It was discovered that children with UIC levels greater than 200 micrograms/L had a higher percentage of anti-TPO positivity. The association between UIC and thyroid autoimmunity was found to have an odds ratio more than 1, indicating that UIC levels greater than 200 micrograms/L were associated with an increased risk of thyroid autoimmunity (Table 5).

Table 1. Distribution of grade of goitre in the study sample

Grade of goitre	**Frequency (%)**
1b	38(51.4%)
2	33(44.6%)
3	3(4.1%)
Total	74(100%)

Table 2. Distribution of FT4 of the study sample

FT4	Frequency	(%)
Decreased	5	6.8%
Normal	66	89.2%
Increased	3	4.0%
Total	74	100%

Table 3. Distribution of TSH of the study sample

TSH	Frequency (%)	P value
Decreased	2(2.7%)	<0.0001
Normal	58(78.4%)	
Increased	14(18.9%)	
Total	74(100%)	

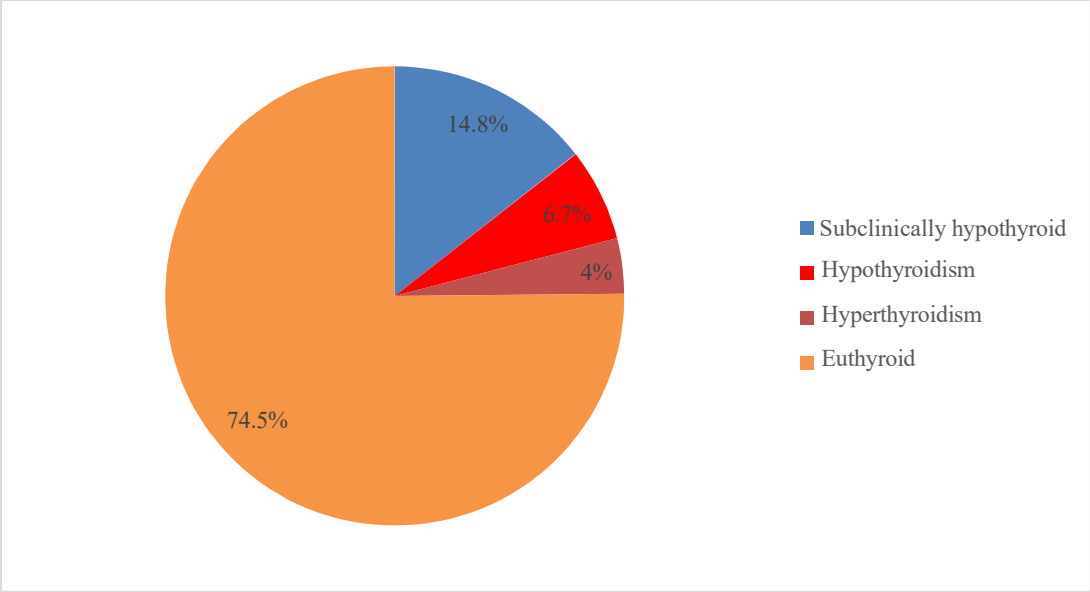


Figure 1. Distribution of thyroid function test

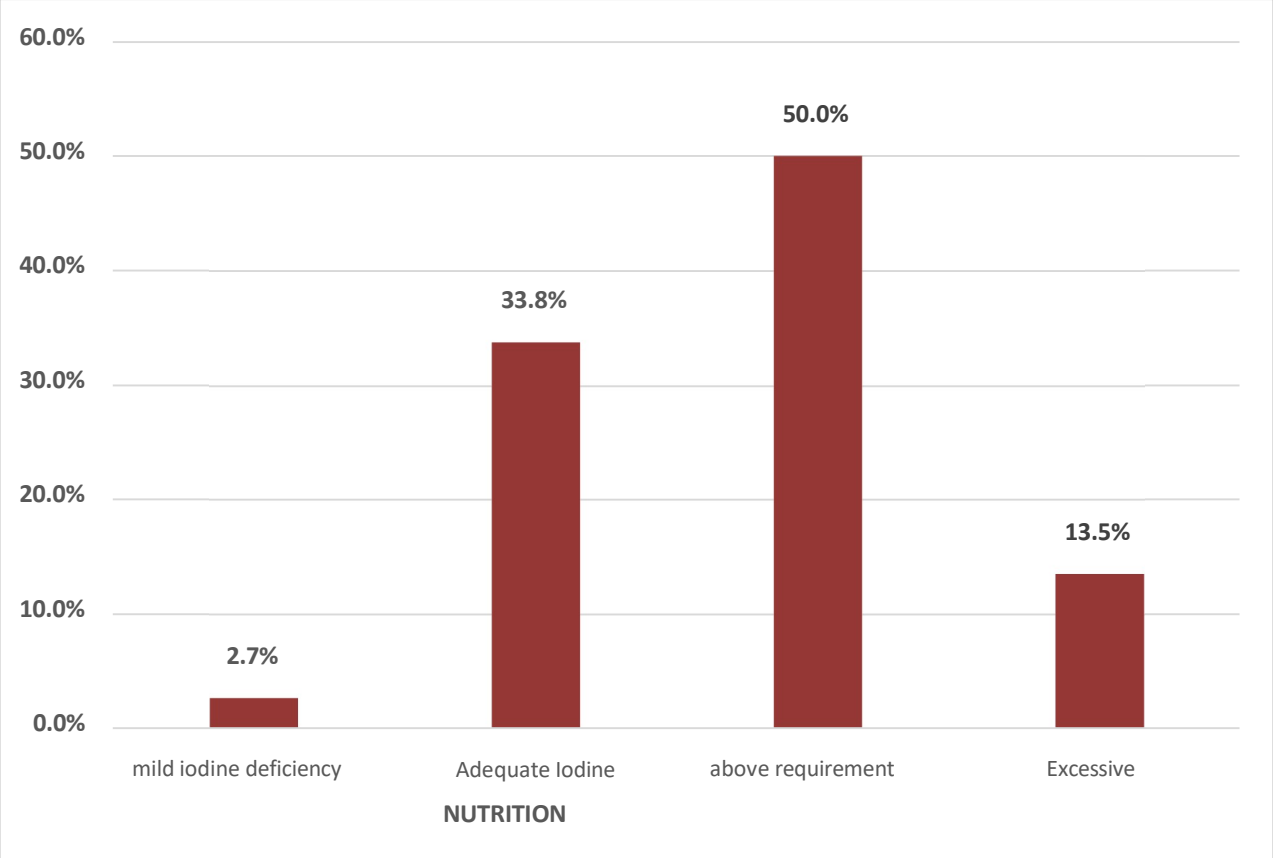


Figure 2. Distribution of UIC

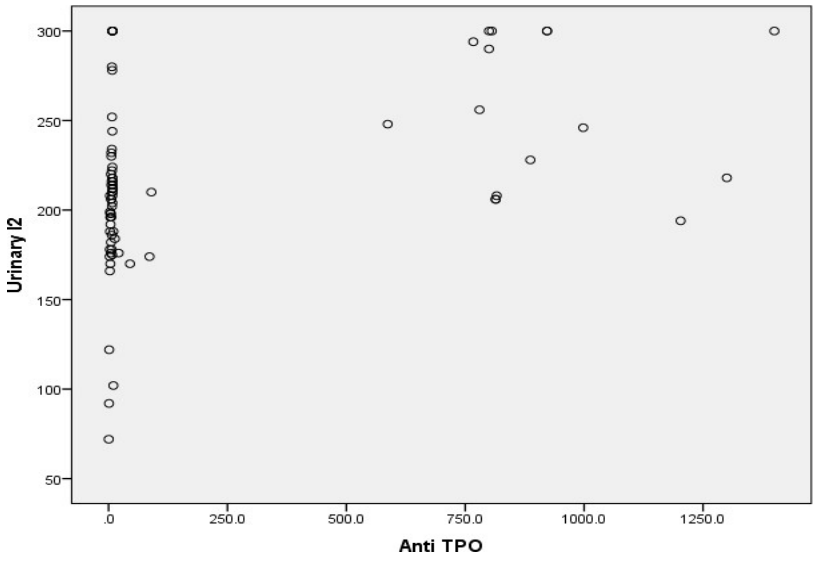


Figure 3. Scatter diagram showing moderately positive correlation between anti TPO and Urinary Iodine Concentration

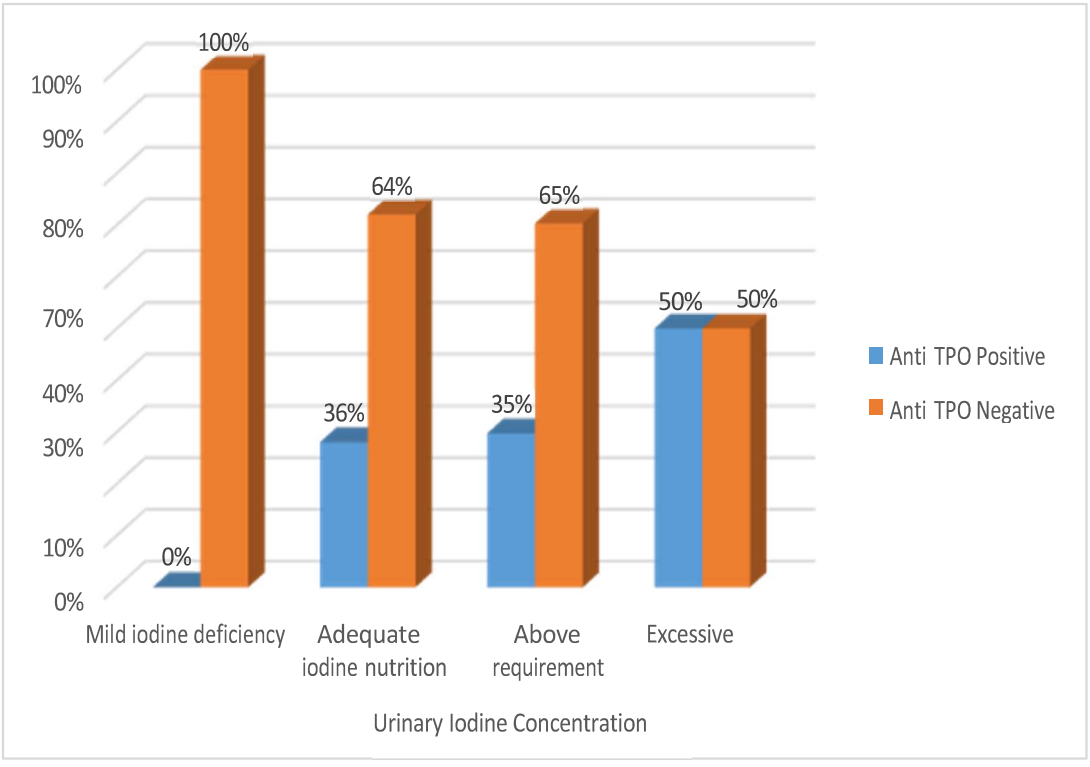


Figure 4. Chart showing relation between thyroid autoimmunity and Urinary Iodine Concentration in the study sample

Table 4. Urinary Iodine Concentration and thyroid dysfunction of the study sample

Urinary Iodine Concentration (micrograms/Litre)				**p value**
		<200	**≥200**	
Euthyroid	Frequency	21	34	0.413
	%	77.8%	72.3%	
Subclinical hypothyroid	Frequency	2	9	
	%	7.4%	19.2%	
Hypothyroid	Frequency	2	3	
	%	7.4%	6.4%	
Hyperthyroid	Frequency	2	1	
	%	7.4%	2.1%	

Table 5. Odds ratio showing relation between UIC and thyroid autoimmunity

			Anti TPO		Odds Ratio	p value
			Negative	Positive		
Urinary Iodine Concentration	<200	Frequency	18	9	1.241	0.6
		%	66.60%	33.40%		
	>200	Frequency	29	18		
		%	61.70%	38.30%		

Discussion

The clinico-epidemiological profile of the goitrous children is defined by our investigation. The children's traits are in line with earlier numerous research that found that girls and adolescents were more likely to develop goitre [1,7]. This study highlights that goitre may run in families. Previous research on goitre has addressed genetic variables [8]. One well-known fact is that goitre can result from dietary iodine deficiency [9]. Although not statistically significant, our discovery that children who consumed more iodine-rich food had higher goitre grades suggests that goitre can be brought on by an overabundance of iodine.

Excessive iodine consumption can result in thyroid autoimmunity, goitre, hyperthyroidism, and hypothyroidism [6]. A significant proportion of children in our study was having anti TPO positivity. Nearly 42% of the goitrous children were having a USG thyroid suggestive of autoimmune thyroiditis whereas only 36.5% of the goitrous children had thyroid autoimmunity depicted in serum. The reason why there is this discrepancy could be that thyroid autoimmunity was determined only using anti TPO positivity. Autoimmune thyroiditis as an etiology for goitre has been appreciated especially in adolescents. Thyroid peroxidase antibodies and thyroglobulin antibodies mark thyroid autoimmunity. This affects around 10% of the general population. Autoimmune thyroiditis has a major impact on the growth and development of children and adolescents [10]. It can cause hypothyroidism, hyperthyroidism, and can predispose to developing thyroid malignancy, lung malignancy, gastrointestinal malignancy and urogenital malignancy [11]. 66% of the children with thyroid autoimmunity had UIC levels above 200 micrograms/liter, which indicates an iodine consumption beyond the recommended level, according to our study. This further clarifies that excessive iodine consumption can cause autoimmune thyroiditis, as does the moderate positive correlation between thyroid autoimmunity and UIC suggests. Furthermore, since the odds ratio is greater than 1, we can conclude that consuming too much iodine may increase the risk of thyroid autoimmunity. According to a study, in Chinese children, excessive iodine supplementation has raised the incidence and severity of autoimmune thyroiditis [12]. The median UIC in our study was 210 micrograms/L wich is higher than that obtained in a study among the school children in Gonda [13]. Given that our sample's median UIC showed an iodine intake over the recommended level, we speculate that coastal regions, where seafood is abundant, may be more susceptible to excessive iodine intake. In a cross-sectional study carried out in Ethiopian schools, Elias et al. found that the children's median UIC was significantly higher above the acceptable threshold (518 micrograms/liter). Additionally, 45.1% of the salt samples were found to be too iodinated. He opined that ensuring homogenous iodization of salt is crucial [4].

Conclusion

Thyroid autoimmunity is a predominant cause for goiter in school children and iodine deficiency is negligible in goitrous children of this coastal area. Thyroid autoimmunity was significantly higher in children with higher iodine intake. In light of our findings, we recommend that iodine intake be closely watched, particularly in coastal regions. A noteworthy achievement in reducing the incidence of goitre and iodine deficiency is the National Iodine Deficiency Disorders Control Programme (NIDDCP). We would like to draw attention to the program's third and fourth goals, which are to conduct resurveys to evaluate iodine deficiency disorders and the effects of iodated salt every five years in the districts and to monitor the iodine content of salt and urinary iodine concentration in laboratories, respectively.

Limitations

There are various limitations to our investigation. We are unable to reach an epidemiological level of recommendation due to the small sample size. To draw any similar findings, more population-based research is required. Because of the patients' financial limitations, we were only able to perform the anti-TPO titre to diagnose thyroid autoimmunity and not the thyroglobulin antibody levels. The source of the consumed excess iodine could not be delineated as a quantitative estimation of the iodine content of diets was beyond the scope of our study.

Statements and Declarations

Ethical Approval

Approval was obtained from the Institutional Ethics Committee (ECR/122/Inst/KL/2013/RR-16). Date and certificate number of IEC clearance- 13/11/2018 ; 42/2018.

Informed Consent

Written informed consent of parent (if the child is below 7 years of age) or assent from the child (if the child is above 7 years of age) was taken. Expenses of the investigations of all the study participants if any, was incurred by the researcher. Confidentiality of the information obtained was assured throughout the study.

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

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