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Thyroid Function and Thyroglobulin Level in Iodine-Deficient Children of Eastern Nepal

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Abstract

Iodine deficiency during childhood affects physical and mental development. Iodine deficiency or excess both can negatively impact thyroid function. We conducted this study to assess iodine nutrition and thyroid function in children with insufficient urinary iodine concentration. A community-based cross-sectional study was conducted among the selected schools of Udayapur district. Urinary iodine concentration (UIC) was measured in 1012 school children (6-14 years). Based on UIC data, 83 blood samples were collected to measure serum thyroglobulin (Tg), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4). UIC was measured by ammonium persulfate digestion method, and Tg, TSH, fT4, and fT3 were measured using ELISA kits. The median UIE was 236 µg/L, and 11.1% of the children had insufficient UIC. The mean fT3, fT4, and TSH in children with insufficient UIC were 2.55±0.43 pg/mL, 0.96±0.28 ng/dL, and 3.60±1.44 mIU/L respectively. Among children with low UIC levels, the median Tg was 17.5 ng/mL. Overt hypothyroidism was seen in 6%, and subclinical hypothyroidism in 3.6%. The children had sufficient iodine nutrition, and the frequency of thyroid dysfunction was low among the children with insufficient UIC.

Keywords: Children; Iodine deficiency; Nepal; Thyroid dysfunction; Urinary iodine concentration (UIC)

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Introduction

Iodine is an essential micronutrient required for the production of thyroid hormones [1, 2]. Iodine deficiency affects 2 billion people, with 36.4% being school-age children [3]. Iodine deficiency during pregnancy and childhood has severe consequences, including developmental disorders, poor cognition, and intellectual disability [4]. Supplementation of iodine in food or salt has led to a significant reduction in iodine deficiency disorders worldwide [5].

Nepal has been continuously improving in iodine nutrition after starting the universal salt iodization program [6-8]. Several studies, particularly in eastern Nepal show promising results in the improvement of iodine deficiency as revealed by an increase in median urinary iodine concentration (UIC) of school children [6-8]. However, there are also concerns about excess iodine intake in such a population [9]. Iodine deficiency or excess both affects thyroid function; therefore, it is important to maintain thyroid function in such a population [1]. Currently, the impact of iodine deficiency on thyroid function and thyroglobulin level in children living in the eastern part of Nepal is unknown. Therefore, in this study, we specifically aimed to find the recent iodine status in a large cohort of school children, and then measure thyroid function in the children with low UIC.

Materials and Methods

Study design

This community-based study was conducted among school children from the Udayapur district of eastern Nepal. The study was conducted by the department of biochemistry in collaboration with the department of pediatrics of B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal. A multistage random sampling technique was used to enroll school children aged 6 to 14 years in the study. Out of 46 village development committees (VDC) in the Udayapur district, four VDCs (Beltar, Basaha, Rampur, and Chaudandi) were randomly selected for study purposes. In those four VDCs, six schools (four schools from 2 VDCs and two schools from the other 2 VDCs) were chosen for sample collection. All the students from those schools in the age range, and fitting into the inclusion criteria were enrolled. A total of 1012 children participated, and in the first stage, 1012 urine samples

Table 1. Iodine status according to gender. The data are expressed as frequency (percentage). A Chi-square test was used between gender and iodine status at a 95% confidence interval. ID= Iodine deficiency

		Severe ID (<20 µg/L)	Moderate ID (20-49 µg/L)	Mild ID (50-99 µg/L)	Sufficient (100-299 µg/L)	Excessive (>300 µg/L)	P value
Gender	Male (n=482)	5 (0.5%)	13 (1.2%)	40 (3.9%)	266 (26.3%)	158 (15.6%)	0.5
	Female (n=530)	4 (0.4%)	19 (1.8%)	31 (3.0%)	291 (28.7%)	185 (18.3%)	
	Total (n=1012)	9 (0.9%)	32 (3.2%)	71 (7.0%)	557 (55.0%)	343 (33.9%)	

were collected from the participants. After UIC measurement, only those children with insufficient UIC (UIC<100 µg/L) were followed up for blood sampling. Blood samples were taken from 83 children out of 112 children with insufficient UIC (UIC<100 µg/L), as 29 children dropped out for blood sampling. Blood samples were collected to assess thyroid function and thyroglobulin level. This study was approved by the Institutional Review Committee of BPKIHS and conducted under the Helsinki declaration of 1975.

Sample collection and analysis

Written informed consent was obtained from the guardian of children prior to participation in the study. All the stakeholders, including participants, were informed about the purpose of the study. All healthy school-going children (aged 6-14 years of age) were included. Children taking drugs that interfere with thyroid function, taking iodine supplements, or with any severe illness were excluded. In the first stage of the study, anthropometric measurements (height and weight) were taken, and spot urine samples were collected from all 1012 participants. Urine samples were collected in a clean, tightly screw-capped plastic vial and transported to the biochemistry laboratory for analysis. In the second phase of the study, blood samples (3ml) were collected in the plain vial by venipuncture following the standard protocol. Clotted blood was centrifuged at 3000 rpm, and serum was separated. Serum and urine samples were refrigerated at -20 °C until analysis. Urinary iodine concentration was estimated by ammonium persulfate digestion microplate (APDM) method using Sandell-Kolthoff's reaction [10]. Serum-free triiodothyronine (T3), free tetraiodothyronine (T4), TSH, and thyroglobulin (Tg) were measured by the ELISA method using commercial kits from Diametra Company.

Based on the reference ranges of thyroid hormones (fT3, fT4, and TSH), thyroid function was classified as normal thyroid function (fT3, fT4, and TSH within the reference range), overt hypothyroidism (TSH above the reference range and fT3 and fT4 below the reference range) and subclinical hypothyroidism (TSH above the reference range, and fT3 and fT4 within the reference range). The reference range followed for fT3, fT4 and TSH were 1.2-4.2 pg/ml, 0.8-2.2 ng/dL, and 0.39-6.16 mIU/L respectively.

Statistical analysis

The data was analyzed using SPSS version 20.0. The data are presented in the form of mean ± SD (for normally distributed variables), median with inter quartiles (IQR) for non-normally distributed variables and frequency (percentage). Age, height, weight, serum fT3, serum fT4 and serum TSH concentration showed normal distribution, so they were expressed as mean±SD. The UIC and serum thyroglobulin levels were expressed as median with IQR as they were not normally distributed. Chi-square test was applied to assess statistical difference among categorical variables (gender versus iodine status, gender versus thyroid function). Spearman's analysis was used to find a relationship between quantitative variables (UIC with thyroid hormones and Tg, Tg with thyroid hormones). A 'p' value of ≤0.05 was considered statistically significant at a 95% confidence interval.

Results

A total of 1012 school children (482 males and 530 females) from 4 VDC of the Udayapur district participated in the study. The mean±SD age, weight, and height were 10.81±2.32 years, 29.04±8.79 kg, and 131.64±14.61 cm respectively. The median UIC with IQR was 236 µg/L (156, 331) indicating adequate iodine intake. The median UIC (IQR) among male and female children were 219 µg/L (149, 335) and 248 µg/L (165, 330) respectively.

Table 1 shows the classification of iodine nutrition status in the study participants according to modified WHO assessment criteria with adequate and more than adequate group merged as sufficient category [3]. The overall prevalence of iodine deficiency based on individual UIC cutoffs was 11.1% (severe, moderate, and mild deficiency). About one-third, (33.9%) of the children had excessive UIC (UIC>300 µg/L).

The mean fT3, fT4, TSH, and median Tg (IQR) in children with insufficient UIC were 2.55±0.43 pg/mL, 0.96±0.28 ng/dL, 3.60±1.44 mIU/L, and 17.5 (12, 29.4) ng/mL respectively. Out of 83 participants with low UIC, 75 (90.3%) had normal thyroid function, 5 (6.0%)

had overt hypothyroidism, and 3 (3.6%) had subclinical hypothyroidism. Among males with low UIC (n=40), 36 (90%) had normal thyroid function, 2 (5%) had overt hypothyroidism, and 2 (5%) had subclinical hypothyroidism. Among females with low UIC (n=43), normal thyroid function, overt hypothyroidism, and subclinical hypothyroidism were seen in 39 (91%), 3 (7%), and 1 (2%) children respectively. No significant differences (p=0.761) in thyroid function was seen between male and female with insufficient UIC.

In the children with insufficient UIC, Tg has positive correlation with fT3 (r=0.273, p=0.013). However, Tg had no significant correlation with fT4 (r=0.012, p=0.916) and TSH (r=0.056, p=0.615). In the same group, there was no significant correlation of UIC with fT3 (r=-0.075, p=0.503), fT4 (r=-0.139, p=0.212), TSH (r=0.175, p=0.114) and Tg (r=-0.075, p=0.503).

Discussion

Iodine deficiency has remained the most common cause of preventable brain damage in children worldwide [11]. Supplementation of iodine in salt through universal salt iodization has become effective in Nepal as shown by improving median UIC in the previous studies from eastern Nepal [6-8]. Median UIC indicates recent iodine intake and is used as a marker of iodine status in the community settings. In the present study, the median UIC was 236 µg/L, which indicates sufficient iodine nutrition among children of this district. The previous report showed a median UIC of 268 µg/L among children of this district [7].

In this study, 11.1% of the children had UIC< 100 µg/L, which is considered iodine deficiency. In the previous study, iodine deficiency in this district was 12.7% [7]. National surveys conducted in Nepal in the years 1998, 2005, and 2007 depicted iodine deficiency in 43.6%, 27.4%, and 19.4% school-age children respectively [12]. In another study in eastern regions, Dhankuta and Dharan, iodine deficiency was 26.6% and 15.6% respectively among school children [13, 14].

Thyroglobulin, a thyroid-specific protein, and precursor in the synthesis of thyroid hormones is considered a sensitive marker of the iodine status than UIC [15]. The median thyroglobulin level in the children with insufficient UIC was 17.5 ng/mL. Our previous study among pregnant women of eastern Nepal reported a median Tg of 6.5 ng/mL [16]. Thyroglobulin increment in plasma is also seen with a thyroid mass, inflammation, and hyperactivity of TSH [17].

We observed normal thyroid function in most of the children with insufficient UIC. Out of 83 children with insufficient UIC, 6% (n=5) had overt hypothyroidism, and 3.6% (n=3) had subclinical hypothyroidism. Previous studies by Shakya et al., Chaudhari et al., and Khatiwada et al. found subclinical hypothyroidism in 19.5% and 16.7 % (in Morang and Sunsari respectively), 31.8% and 25.59% (in Sunsari and Dhankuta respectively) and 17.6 % respectively (in hilly regions) [18, 14, 19]. Low prevalence of thyroid dysfunction in the current study than previous studies may be due to differences in the geographic location, genetic factor, and small sample size of the current study. In the current study, one-third (33.9%) of the children had excessive UIC, which suggests the risk of iodine-induced hyperthyroidism and autoimmune thyroid disease in those children. Future studies need to investigate the effect of excessive iodine consumption on thyroid function. Furthermore, the salt iodine fortification level may need to be readjusted to lower iodine intake in the community. Interestingly, our finding of a low rate of thyroid abnormalities in children with insufficient UIC suggests that the thyroid gland can adapt to low iodine intake. Moreover, UIC is an indicator of recent iodine intake, and it does not reflect long-term iodine nutrition in those children with insufficient UIC. In addition, the coexistence of autoimmune thyroiditis also contributes to abnormal thyroid function in the community. Overall, thyroid function can be impaired both in the condition of iodine deficiency and excess, and therefore, maintaining optimal iodine intake by continuous monitoring of dietary iodine intake and UIC is crucial [1].

We observed a non-significant negative correlation of UIC with Tg level and thyroid hormones in children with insufficient UIC, and a positive correlation between thyroglobulin and fT3 (r= 0.273, p=0.013). In iodine-deficient cases, thyroglobulin tends to rise due to hyperactivity of the thyroid gland and TSH; however, the thyroid gland may be able to adapt to short-term iodine deficiency maintaining normal thyroid hormones [1]. The present study has several limitations. Individual UIC was used as a marker of iodine deficiency, and thyroid function was not assessed in all the participants. Thyroglobulin was estimated in the children with low UIC, and other common causes of thyroid dysfunction such as autoimmune thyroiditis were not investigated. Future studies need to consider several of these factors.

Conclusion

Sufficient iodine nutrition occurs among the school children of the Udayapur district, with one-third of the children having excessive UIC, and a small proportion having insufficient UIC. The incidence of thyroid dysfunction is low in children with insufficient UIC. Future studies need to be undertaken to measure thyroid function in children with excessive UIC, and other potential causes of hypothyroidism in children with insufficient UIC need to be investigated.

Abbreviations

APDM: Ammonium persulphate digestion method
Free T4: Free thyroxine
Free T3: Free triiodothyronine
Tg: Thyroglobulin
TSH: Thyroid-stimulating hormone
UIC: Urinary iodine concentration

Author contributions

SK1, SK2, BG, NB, and ML designed the study. SK1 and ST collected the samples. SK1 analyzed the samples. SK2 performed data analysis and drafted the manuscript. SK1 helped in drafting the manuscript. All authors read and approved the final version of the manuscript.

Competing interests

None

Funding

None

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Ethics approval and consent

The study was approved by the Institutional Ethical Review Committee (IRC) of BPKIHS (Code No: IRC/422/014). Written consent was taken from children's parents before participation.

Availability of data and material

Data are available on reasonable request.

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