Journal of Environmental Science and Technology

ISSN 1994-7887

science alert

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OPEN ACCESS Journal of Environmental Science and Technology

ISSN 1994-7887
DOI: 10.3923/jest.2020.131.138

Research Article
Thyroid Dysfunction among School-Aged Children due to Chronically Excessive Iodine Groundwater, Central Java, Indonesia

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Abstract

Background and Objective: Iodine excess is a risk factor in thyroid dysfunction. The purpose of the study was to identify the prolonged effect of iodine excess on thyroid dysfunction in areas with high iodine on natural resources in Indonesia. **Materials and Methods:** A cross-sectional study was conducted in two districts. This study included 500 School-Aged Children (SAC) 06-12 years of age for 25 clusters in each district, were included in this study. Logistic regression was performed to estimate the risk of thyroid dysfunction. **Results:** Demak and Grobogan were classified as iodine excess area with Median Urine Iodine Concentration (MUIC) is 446, 453 μg L^{-1}, iodine water at 112.3, 414.5 ppb. Profile thyroid dysfunction was described as subclinical hypothyroidism, 31.5, 36.3%, secondary hypothyroidism, 25.5, 6.9%, respectively. While autoimmune thyroiditis was not shown, overt and subclinical hyperthyroidism was found in Grobogan only 0.4;1.4%. Excess iodine raises the risk of subclinical hypothyroidism, Adjusted Odd Ratio (AOR): 1.97 (CI:1.1-3.4) and secondary hypothyroidism, AOR: 2.44 (CI:1.5-3.9). **Conclusion:** Subclinical hypothyroidism is the most prevalent thyroid disease in iodine excess area due to elevated iodine in groundwater.

Key words: Iodine excess, water, school-aged children, thyroid function disorder, elevated iodine, hypothyroidism

Citation: Kusrini, I., M. Samsudin, P. Broto, S. Kumorowulan, S. Supadmi and A.D. Laksono, 2020. Thyroid dysfunction among school-aged children due to chronically excessive iodine groundwater, Central Java, Indonesia. J. Environ. Sci. Technol., 13: 131-138.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Iodine is an essential micronutrient for thyroid function that controls several important human metabolism processes[1] that have been transferred to the human body via dietary intake. Iodine was needed in certain quantities[2]. Deficiency or excess iodine can, therefore, interfere with the synthesis of thyroid hormones such as U-shapes[3].

Iodine is accessible by nature. Through a biogeochemical cycle, iodine from the oceans is released into the atmosphere and falls with rainwater and then infiltrates into the soil. This can also contribute to a difference in the iodine content of various geomorphological environments[4-6]. The mountainous areas with a certain slope have a very low iodine level, with a possible risk of iodine deficiency[4]. The previous research established the association between natural iodine content (geographic variation), iodine status and thyroid function disorder[7,8]. Mountainous areas have been recognized as goiter endemic areas in the past due to lack of iodine, but it has been seen in the time before the introduction of the iodine deficiency control strategy.

Conversely, there is a special geomorphological type known as having a high content of natural iodine[9–11]. Previous studies have shown that high iodine in groundwater is the most indicator of iodine excess in some regions[12]. However, another source of iodine excess that has been acquired. The median concentration of urinary iodine (UIC) was significantly increased following the introduction of the Salt Iodization (USI) program[13]. Another study reported iodine excess was affected by high dietary iodine intake. Japan has described the intake of seaweed as a risk factor for iodine excess[14].

Grobogan and Demak Regency are distinct geomorphological sites with a high degree of iodine in groundwater. The 2003 National Iodine Survey and the 2007 National Basic Health Study Sub-sample reported a median concentration of urine in both areas of more than 300 μg dL^{-1} with iodine excess prevalence in school-aged children >70%[15]. A previous study found iodine excess determinants are high iodine content in groundwater in both areas[16].

Iodine in groundwater was thought to be a long-term natural reaction to excess iodine. Though the mechanism of adaptation in the human body to counter high exposure to iodine was unclear. The link between iodine excessive consumption and thyroid dysfunction as an acute effect was established, but the chronic effect of long-term iodine excess is still unclear, especially as regards iodine excess due to high iodine in Central Java groundwater. The objective of this study was therefore to identify the type of thyroid dysfunction that has occurred in areas with iodine excess area due to iodine-rich groundwater content.

MATERIALS AND METHODS

Study area: The study was a cross-sectional study in two districts identified as iodine excess area from January to November 2016 that include 500 School-Aged Children (SAC) 06-12 years of age, in 25 clusters of each district. Iodine status was defined by median Urinary Iodine Concentration (UIC) using spectrophotometric methods. Thyroid function was assessed by thyroid-stimulating hormone (TSH) and free thyroxine (FT4) using human reagent Elisa. Data analysis was administered using SPSS 21.

Study design: This cross-sectional research was conducted in school-aged children 6-12 years of age living in two districts of Central Java known as the iodine excess area.

Setting: School-aged children were considered to be indicative of the iodine population in the iodine-excess region due to high iodine in groundwater. Iodine excess area: two districts previously identified as iodine excess area, as recorded in the 2003 iodine survey results, national basic health research and previous review.

Participant and study size: The sample of this study was school-aged children 6-12 years of age living in iodine-excessive areas. The inclusion criteria for all subjects are as follows: 1. School-aged children living in this district for a total of two years; 2. No chronic diseases reported; 3. no exposure of iodine capsules in the last five years. Eligible samples were identified using a two-stage cluster sampling process. The 25 clusters were used and the village was considered to be a cluster. Simple random sampling was used to select a subject from the sampling frame in each cluster.

The Lemeshow formula for estimating the proportion with absolute precision was used to estimate the minimum sample size per area. Therefore, 250 samples of each district were taken and 500 samples of the iodine excess region. Weight was used to verify the cluster test for the standardized estimated prevalence of iodine excess and thyroid function in two iodine excess districts with 80 percent power and 10 percent error[17].

Variables: Iodine status in school-aged children was assessed by the concentration of urinary iodine (UIC) as exposure variables. The dietary source of iodine was calculated to be iodine in water, while the amount of water ingested was expected to be converted to sodium in the urine. The dietary pattern of daily food using a food frequency questionnaire to take the source of iodine in water and food. Such variables were also taken as treatment variables. Thyroid function was assessed by the concentration of Thyroid-Stimulating Hormone (TSH) and free thyroxine hormone (FT4) in blood samples for outcome variables.

Study procedures and laboratory measurements

Urine samples: Urine samples were taken: spot samples to estimate urinary iodine concentration (UIC) and 24 h a day samples to estimate Urinary Iodine Excretion (UIE). Urinary iodine analysis was performed based on a Sandell-Kolthoff reaction with ammonium persulphate digestion. Laboratory analyses were conducted in the Indonesia National Health Research and Development Unit Laboratory in Magelang (Indonesia, Balai Litbangkes Magelang) that have successfully participated in the Ensuring Quality of Urinary Iodine Procedure (EQUIP) scheme (U.S. Center for Diseases Control And Prevention, Atlanta).

Blood samples: Serum was also collected from school-aged children to test thyroid function dysfunction via a combined diagnosis of thyroid-stimulating hormone (TSH) and free t4, as determined by the Enzyme-Linked Immunosorbent Assay using the German Human Reagent Kit. Before an examination, the serum was isolated by centrifugation. All analyzes were performed at the Indonesian National Health Research and Development Laboratory in Magelang (Indonesia, BP2GAKI Magelang).

Thyroid dysfunction: The standard reference range for TSH was 0.3-5 mIU L^{-1}. The analysis of FT4 matched the reference range of the human reagent kit 0.8-2.0 ng dL^{-1}. The following diagnostic criteria were used to assess the prevalence of thyroid dysfunction in the sample population: subclinical hypothyroidism: elevated TSH, normal FT4; overt hypothyroidism: elevated TSH and low FT4 or TSH >10 mU L^{-1} and normal FT4; subclinical hyperthyroidism: low TSH and normal FT4; overt hyperthyroidism: low TSH and elevated FT4; isolated hypothyroxinemia: normal TSH and low FT4, secondary hyperthyroidism was excluded from thyroid disease in this study.

Dietary iodine intake: Household salt samples were collected in a plastic jar to determine the iodine content using the titration process. Salt intake was predicted by the conversion of the sodium content in salt measured in the urine of the subsamples.

Bias: There was no potential biased was detected in this analysis.

Quantitative Variable and Statistical Method: Data were verified for normality using the Kolmogorov Smirnov method. If data were not usually distributed, non-parametric tests (Spearman) were used to analyze the association between exposure variables and outcomes. So while the normal distribution was obtained, and parametric tests was used. Median iodine urine was measured using a complex sample method to explain the level of iodine in the population. Multivariate analysis was performed to control confounding factors and to adjust the risk (AOR) of thyroid function disorder associated with all risk factors for iodine excess area die to high iodine in water using logistic regression. Data management and data analysis were performed using licensed SPSS 21 from IBM.

The study and all procedures were approved by the Indonesian Health Research and Development Ethics Committee. All participants provided written informed consent before participation. Data collection was carried out from January to November 2016.

RESULTS

The findings showed that in the Demak and Grobogan districts, iodine status in school-aged children was classified as iodine excess, with a median urinary iodine concentration (MUIC) of 446 and 453 μg L^{-1}, respectively (Table 1). Moreover, average levels of the thyroid hormone TSH, FT4 and also of the iodine storage indicator (Thyroglobulin) in the normal range in both areas (Table 2). This means that the population of both countries has a natural thyroid hormone despite the living of countries of excessive iodine abundance.

Table 1: Iodine status of school-aged children in Iodine excess area

	Demak		Grobogan	
Parameter	Spot urine (N: 247)	24 h urine (N: 105)	Spot urine (N: 248)	24 h urine (N: 113)
MUIC	446	480	453	496
Minimum	26	122	11	76
Maximum	7750	4980	9850	3140

MUIC: Median urine iodine concentration

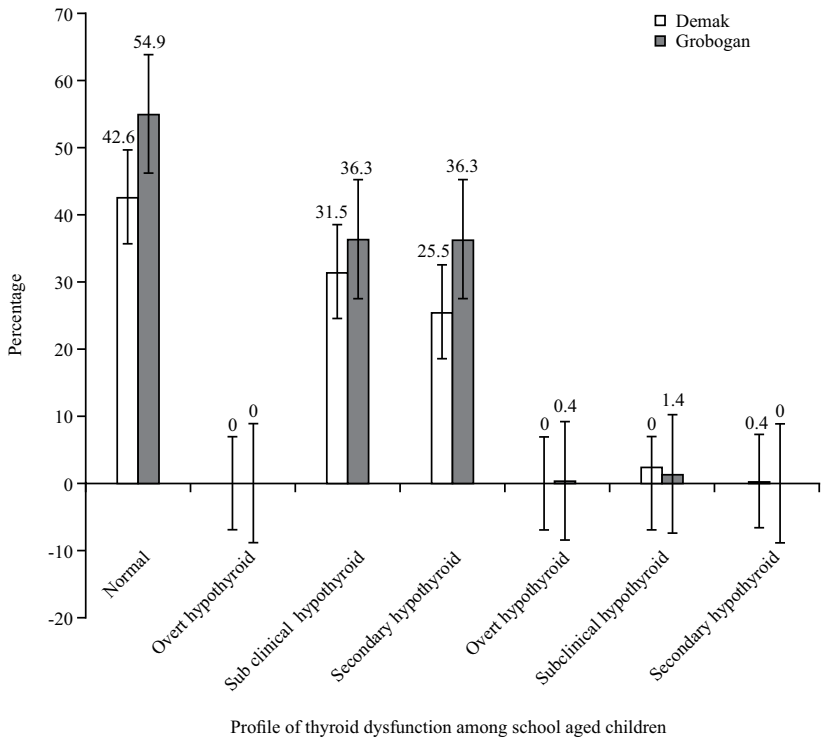

Fig. 1: Thyroid function disorder of school-aged children in iodine excess area

Table 2: Thyroid hormone of school-aged children in Iodine excess area

	Demak (N: 105)			Grobogan (N: 113)		
Parameter	TSH	FT4	Tg	TSH	FT4	Tg
Mean±SD	3.62±2.4	1.79±0.3	15.4±17.8	3.47±1.9	1.78±0.2	24.14±75.8
Median	2.97	1.79	14.7	2.99	1.81	14.7
Min	1.05	0.73	0.73	0.40	1.24	2.31
Max	16.26	2.57	133.9	16.82	2.25	809.1

TSH : Thyroid Stimulating Hormone, FT4: Free thyroxin, Tg: Thyroglobulin, SD: Standard deviation

Table 3: Autoimmune thyroiditis in subsamples of school-aged children in Iodine excess area

	Demak (N: 44)			Grobogan (N: 53)		
Parameter	Positive	Equivocal	Negative	Positive	Equivocal	Negative
Demak	0	6.2	93.8	0	0	100
Grobogan	0	10.3	89.7	0	0	100

Thyroid dysfunction was found in both areas and the most common is subclinical hypothyroidism in Demak and Grobogan, respectively 31.5 and 36.3%. Otherwise, the secondary hypothyroidism with a normal level of TSH but free thyroxine hormone below the normal level is 25.5 and 6.9%, respectively. Overt hyperthyroidism and subclinical hyperthyroidism were observed at very low prevalence of 0.4 and 1.4% and were found only in Grobogan (Fig. 1).

Depending on the thyroglobulin test shown, the prevalence of thyroid function disorders in both areas was shown to be below 10%, thyroid function disorder 7.7% in Demak and Grobogan 3.9% (Fig. 2). No autoimmune thyroiditis has been shown, which is demonstrated by the absence of positive respondents experiencing autoimmune thyroiditis based on anti-Tg and anti-TPO serum measurements (Table 3). Generally, iodine excess raises the risk of subclinical hypothyroidism 1.97 (CI:1.1-3.4) and secondary hypothyroidism 2.4 (CI:1.5-3.9) as shown in Table 4. Yet no one was diagnosed with overt hypothyroidism in both regions.

Table 4: Urine Iodine Concentration and risk of thyroid dysfunction type on school-aged children

	hypothyroidism in Demak and Grobogan (Both areas)							
	Subclinical		Overt and secondary		Subclinical		Overt and secondary	
Parameter	ρ (AOR)	95% CI	ρ (AOR)	95% CI	ρ (AOR)	95% CI	ρ (AOR)	95% CI
UIC>300 μg dL^{-1}	0,01 (1.9)	1.1-3.4	0.00 (2.4)	1.5-3.9	0.01 (0.3)	0.1-0.8	0.79 (0.7)	0.1-5.5
UIC<300 μg dL^{-1}								

AOR: Adjusted odd ratio, CI: Confidence interval, UIC: Urine iodine concentration

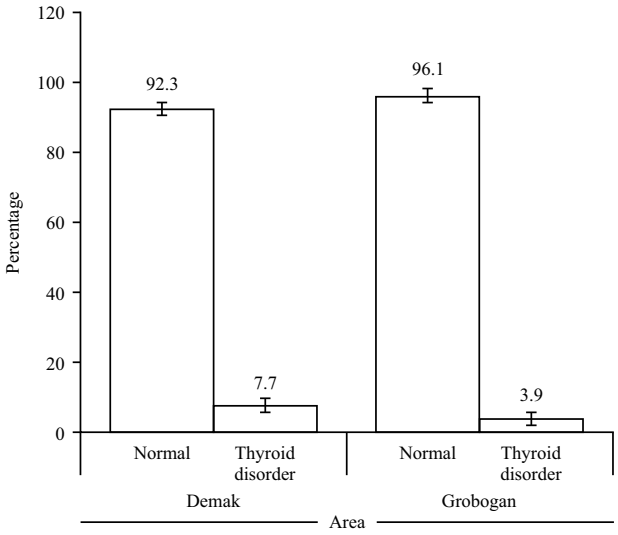

Fig. 2: Thyroid disorder based on thyroglobulin measurement of school-aged children in iodine excess area

DISCUSSION

Prolonged iodine excess is assumed to be linked to thyroid dysfunction. The present research has shown that iodine excess raises the prevalence ratio of subclinical hypothyroidism and secondary hypothyroidism was 1.97 and 2.5 times, respectively. This is similar to the 5-year longitudinal study in China that high iodine intake raises the incidence and prevalence of subclinical and autoimmune hypothyroidism thyroiditis[17]. However, autoimmune thyroiditis has not shown in this study. The previous study showed median UIC 261 μg L^{-1} in Rongxing District and 145 μg L^{-1} in Chengsan and the presence of iodine excess was correlated with an increased incidence of subclinical hypothyroidism[18]. Another research in China at a different location also reported more than sufficient intake of iodine that increase subclinical hypothyroidism[4].

The association between iodine excess caused by high dietary intake and thyroid function disorder was also established in the previous study in Japan, that showed about the determinant of iodine excess due to dietary consumption of seaweed. Subclinical hypothyroidism is the most common thyroid disorder that has been developed[14]. Whereas another study estimated the average intake of algae in Japan was 1.2 mg/day[19]. A case-control analysis in two cities in India indicates that excess iodine is a risk of hypothyroidism, generally[20].

Iodine excess increased prevalence of subclinical hypothyroidism, goiter and elevated thyroid peroxidase antibody was observed in workers in West America after cessation of the iodine-based water filtration method[21]. Many defects in thyroid activity have decreased following the elimination of excess iodine from the drinking water supply. A research conducted by Shengmin in 2013 in areas with high levels of iodine water in China showed some action to minimize the impact of iodine excess on thyroid function. They stopped using iodized salt in children 8-10 years of age for 1.5 years and the findings showed that the median level of iodine in urine decreased from 518 to 416 μg L^{-1} with goiter prevalence from 32.96 to 6.54%, while the prevalence of iodine excess decreased from[22] 82.4 to 63.7%.

Iodine excess raised the abnormality in thyroid activity, several of which are subclinical hypothyroidism. The temporary mechanism of the Wolff-Chaikoff effect may explain that the thyroid gland induces blockage as a reaction to block the entry of excessive iodine[23,24]. Wolf and Chaikoff[25] reported a decrease in the organic binding of iodide in the thyroid hormone when plasma iodide was increased in 1948. As a result, iodide transfer to the thyroid reduces given the acute impact for just two days. Due to the autoregulation of Sodium iodide symporter (NIS). Eng *et al.*[26] proceeded to examine the prolonged administration of excess oral iodide to thyroid function within 6 days. The findings indicated an acute and persistent decline in NIS, mRNA and protein thyroid disease. It also contributes to reduced transport of iodide to the thyroid. Thus, people who do not have a goiter have a tolerance of up to 30 mg of iodine up to 2 g of iodine per day, without clinical symptoms, while they experience a rise in TSH or a decrease in FT4 but still within the normal range via the NIS adaptation process[23,24].The study shows that Wolff-Chaikoff's adaption mechanism was occurred not only in population with acute high iodine intake but also in areas with a history of prolonged iodine excess.

Many measures for calculating iodine intake include thyroglobulin and thyroid gland volume[27]. Thyroglobulin levels in serum suggest iodine reserves in the thyroid gland that are normally followed by enlargement of the thyroid gland[28]. The present study indicated an irregular thyroid function condition below 10%. However, tests using thyroglobulin cannot demonstrate thyroid function disorders caused by a thyroid hormone deficiency or excess thyroid hormone. Some studies have shown that the relationship between iodine excess will increase the volume of the thyroid gland[29–31].

The present research showed that there was no autoimmune thyroiditis in the subsample that was tested. Conversely to laboratory studies that examine the impact of chronic iodine overload on thyroid function and autoimmune events in mice, it can be shown that the iodine overload that exists induces goiter enlargement., Where there is a positive correlation between the dose of iodine given and the amount of thyroid gland. High iodine destroys the epithelial cells of the thyroid and induces thyroiditis[18]. The increased risk of disorders triggered by the autoimmune thyroid gland (autoimmune thyroiditis) is mostly seen in areas with chronic iodine excess[32-34].

Research in Hokkaido Japan, which was known to eat significant quantities (over 200 mg) of seaweed, found that iodine-induced hypothyroidism was caused by autoimmune thyroiditis[35-37]. Iodine excess caused autophagia suppression and associated with Hashimoto's thyroiditis[38]. Another type of autoimmune thyroiditis in iodine excess region is Graves disease, which has been reported in some studies but is a small prevalence. Graves disease is an autoimmune that stimulates the thyroid receptor antibody that is a common cause of hyperthyroidism. Nevertheless, Graves' disease has been affected by many factors, such as biology, social influences and environmental factors[33,38,39].

The findings of this analysis also provide evidence that iodine excess does not associate with the occurrence of both chronic and subclinical hyperthyroidism. It is in line with there search by Yang *et al.*[18] in China that it can be shown that excess iodine has not been shown to raise the incidence of hyperthyroidism. Increased intake of iodine in populations initially experiencing iodine deficiency may cause iodine-induced hyperthyroidism[3,40]. Commonly, after iodine deficiency in a long time, it occurred in individuals who already had a goiter[23]. The previous research in the replete region of the mountainous area in Indonesia also reported iodine-induced hyperthyroidism obtained in the population[41].

CONCLUSION

This study concludes that the most prevalent type of thyroid dysfunction performed in iodine excess area due to high iodine content in groundwater in Indonesia is subclinical hypothyroidism, while it is a physiological mechanism for adapting high exposure to natural resources.

SIGNIFICANCE STATEMENT

This study discovered the profile thyroid dysfunction in iodine excess area is subclinical hypothyroidism and secondary hypothyroidism. But the most prevalent is subclinical hypothyroidism that shows normal mechanism adaption of iodine excess due to natural resources. These results may be beneficial to the strategy to prevent iodine deficiency disorders and to ensure compliance with iodine excess effects, particularly in vulnerable populations. The last sentence of this statement could be as supporting evidence of subclinical hypothyroidism in iodine excess area. This study will help the researchers to uncover the critical areas of profile thyroid dysfunction in iodine excess area due to natural resources in central java that many researchers were not able to explore.

ACKNOWLEDGMENT

The authors wish to thank Dr. Basuki Budiman for his helpful comments in the study report.

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