Journal of Trace Elements in Medicine and Biology 78 (2023) 127172

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Serum thyroglobulin as a biomarker of iodine excess and thyroid disease occurrence in adults

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ARTICLE INFO

Keywords:
Thyroglobulin
Water iodine
Excessive iodine
Biomarker

ABSTRACT

Background: Thyroglobulin (Tg) is considered a sensitive indicator of iodine deficiency. However, the usefulness of Tg as a biomarker of excess iodine is uncertain. The present study aimed to determine the influence of different iodine intake on serum Tg levels, evaluate the influence of thyroid diseases on the distribution of Tg, and identify the factors that may affect Tg levels.

Methods: A cross-sectional survey with a total of 1208 adults was conducted in different water iodine areas in China. Urinary iodine concentration (UIC), water iodine concentration (WIC), serum Tg, thyroid-stimulating hormone (TSH), and thyroid antibodies were measured. The thyroid volumes and nodules were measured by B-scan ultrasound.

Results: Based on the WIC data, subjects were divided into three groups. Based on the median urinary iodine concentration (MUIC) data, the iodine levels were adequate, more than adequate, and excess for the WIC < 10 μg/L group, 10 μg/L $\leq$ WIC $\leq$ 100 μg/L g, and WIC $>$ 100 μg/L groups, respectively. The median Tg was significantly higher in the excess iodine group than in the adequate iodine group and the more than adequate iodine group (14.6 μg/L vs.12.7 μg/L, $P = 0.042$; 14.6 μg/L vs.12.5 μg/L, $P = 0.004$). Multiple linear regression analysis showed that excess iodine intake, goitre, thyroid nodules, and hypothyroidism were significantly related to higher serum Tg levels.

Conclusion: Serum Tg level can be a promising biomarker of excessive iodine intake, but other factors, especially the presence of thyroid disease, should be considered when using this parameter.

1. Introduction

Iodine is a micronutrient that is required for the synthesis of thyroid hormones, which are indispensable for normal growth and foetal brain development in humans [1,2]. Previous studies have elucidated that both iodine deficiency and excess can lead to thyroid diseases [3,4]. Iodine deficiency disorders (IDD) have been prevalent in the past. The universal salt iodization (USI) policy has been implemented for more than two decades in China, resulting in excellent IDD prevention as IDD has been eliminated since 2000 [5]. China has unique geological conditions, and its water iodine varies greatly across the mainland. Many people reside in areas with high iodine levels in drinking water [6]. Up to 1050 towns have water iodine levels greater than 100 μg/L, and more than 40 million residents in these towns are exposed to excess iodine and are at higher risk for thyroid disease [7].

Several indicators have been used in the surveillance of population iodine status, including median urinary iodine concentration (MUIC) and the goitre rate; however, these indicators have some flaws. For example, there is a large degree of variability in individual urine iodine concentration, and it only represents the amount of dietary iodine that was consumed 24 h prior [8,9]. Our previous studies have demonstrated that the goitre rate of adults is not sensitive to excess iodine intake [3,

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https://doi.org/10.1016/j.jtemb.2023.127172
Received 27 November 2022; Received in revised form 2 April 2023; Accepted 3 April 2023
Available online 5 April 2023
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10]. Thyroglobulin (Tg) is another iodine status indicator recommended by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) [11]. Tg is the protein precursor of thyroid hormones, which are essential for growth, development and the control of metabolism in vertebrates [12]. Serum Tg is usually used as a marker for thyroid carcinoma surveillance after lobectomy [13]. Serum Tg has been demonstrated to be sensitive to iodine deficiency, and it is considered a promising biomarker of iodine deficiency [14–17]. The usefulness of Tg as a biomarker of excess iodine is uncertain. The association between iodine excess and Tg level has been evaluated in a previous study, however, the sample size was small and the population was divided by MUIC [18]. The aim of the present study was to determine the influence of different iodine intake on serum Tg levels, to evaluate the influence of thyroid diseases on the distribution of Tg, and to analyse the factors that may affect Tg levels. Meanwhile, we aimed to confirm the hypothesis that serum Tg could be a biomarker of excess iodine intake in adults.

2. Materials and methods

2.1. Study sites and subjects

This cross-sectional study was conducted from May 2019 to June 2019. According to recent national water iodine surveillance data, this study selected Xieyuanji village, Jiucheng village, Yangying village, and Wangfang village in Heze, as well as Dongding village in Jining, Shandong Province where different water iodine concentration (WIC) levels exist and non-iodized salt rather than iodized salt is supplied to residents. These areas of Shandong Province are representative of Chinese iodine excess areas resulting from water, which are historical Yellow River flushing areas. The frequent change in the riverway throughout history has caused the sediment in the flood plain to have excess iodine in water and soil, which is the main reason for the high WIC wells [19]. The inclusion criteria were subjects who had been living in the selected regions for at least 5 years and were between 18 and 60 years old. The exclusion criteria for the participants were as follows: 1) used thyroid medications or iodine-containing supplements; 2) were TgAb positive; or 3) had missing basic information. Strict inclusion and exclusion criteria were applied to this study. First, 1344 subjects were enrolled in this study, but 136 participants were excluded (3 participants used thyroid medications; 5 participants were missing key values, such as age or thyroid ultrasound; and 128 participants were TgAb positive). Finally, a total of 1208 participants were included in this study.

2.2. Questionnaire and physical examination

A standard questionnaire was designed to obtain demographic information, including name, sex, age, personal or family history of thyroid disease, smoking habit, medicine intake, source of drinking water, and drinking duration. Weight and height were measured in kilograms and centimetres, respectively, and the body mass index (BMI) was calculated by dividing the weight (kilograms) by the square of the height ($meters^2$).

2.3. Drinking water and urine sample collection and determination

Each participant provided a water sample. Each water sample was collected in a 25 mL sterile tube and kept at 4 °C until analysis. The drinking WIC was determined with the As^{3+}-Ce^{4+} catalytic spectrophotometry method [20]. Nonfasting spot urine samples were collected from each participant between 7:00 a.m. and 10:00 a.m. Each urine sample was at least 5 mL and was collected in a plastic tube and stored at − 20 °C. The urinary iodine concentration (UIC) was determined with the As^{3+}-Ce^{4+} catalytic spectrophotometry method according to the China Health Standard Method (WS/T107.1–2016) [21].

2.4. Coverage rate of iodized salt

Each participant submitted a sample of table salt (at least 50 g) taken from home, and the iodine content in the salt was examined using a semiquantitative kit for determining iodized salt. Table salt with an iodine content of less than 5 mg/kg was defined as non-iodized salt.

2.5. Thyroid ultrasonography

Thyroid ultrasonography was performed by an experienced examiner using a 7.5-MHz transducer. The thyroid lobe volume was obtained by measuring the depth (d), width (w) and length (l) of each lobe and calculating the volume with the following formula: V (mL) = 0.479 × d × w × l (mm)/1000. The thyroid volume was recorded as the sum of both lobes.

2.6. Blood sample collection and analysis

Fasting blood samples were collected from the cubital veins of the participants in the morning and stored in a glass tube. The serum samples were prepared by centrifugation (3000 r/m, 10 min) after standing for an hour and were frozen at − 80 °C. The frozen serum samples were then transported to Harbin Medical University in Heilongjiang Province and were stored in a − 80 °C freezer until analysis. Serum thyroid-stimulating hormone (TSH), thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb), and Tg were evaluated using a chemiluminescent immunoassay (Roche Diagnostic GmbH, Germany) at the Fourth Affiliated Hospital of Harbin Medical University. The method of testing Tg has been standardized against Certified Reference Material (CRM) 457 of the Community Bureau of Reference (BCR) of the European Union. The reference ranges were as follows: TSH, 0.27–4.20 μIU/mL; TGAb, 0–115.0 IU/mL; TPOAb, 0–34.0 IU/mL; and Tg, 3.0–40.0 μg/L [22].

2.7. Diagnostic criteria for thyroid diseases

There were several diagnostic criteria for thyroid diseases. A goitre was defined as a thyroid volume > 25 mL for men and > 18 mL for women [23]. A thyroid nodule with a maximum diameter of > 3 mm was registered. Hypothyroidism, including clinical hypothyroidism and subclinical hypothyroidism, was defined as TSH > 4.20 μIU/mL. Hyperthyroidism, including clinical hyperthyroidism and subclinical hyperthyroidism, was defined as TSH< 0.27 μIU/mL. Elevated Tg was defined as Tg > 40 μg/L.

2.8. Statistical analysis

Data were recorded using Microsoft Office Excel 2010, and statistical analysis was performed using IBM SPSS statistics version 19. The Kolmogorov–Smirnov method was used to test normality. The data with a normal distribution are presented as the mean ± standard deviation (mean ± SD), and the nonnormally distributed data are presented as the median with 25th and 75th percentiles. Comparisons of sub-data among different groups were completed by using one-way ANOVA for normal and continuous variables as well as nonparametric rank test (Kruskal–Wallis test) for nonnormal and continuous variables. Comparisons between two groups were completed using the Mann–Whitney U test for nonnormal and continuous variables. A comparison of the proportions among three groups was performed by the chi-square test or Fisher's exact test. Spearman's rank correlation was used to examine the correlation between Tg and other factors. A multiple linear regression model was performed to identify the determining factors of serum Tg. Binary logistic regression analysis was conducted to calculate the odds ratio (OR) and 95% confidence intervals (CIs) for elevated Tg by iodine nutrition status and other risk factors. A P value of < 0.05 was considered statistically significant.

3. Results

3.1. Description of the study population and division into the groups according to the WIC

Based on the WIC data, the participants were divided into three groups as follows: WIC < 10 μg/L group; 10 μg/L ≤ WIC ≤ 100 μg/L group; and WIC > 100 μg/L group. The detailed iodine concentrations in the drinking water and urine of the three water iodine groups were presented in Table 1. The following iodine nutrition criteria were provided by the WHO [11]: deficient, MUIC< 100 μg/L; adequate, 100 μg/L ≤ MUIC < 200 μg/L; more than adequate, 200 μg/L ≤ MUIC < 300 μg/L; and excess, MUIC ≥ 300 μg/L. Based on the MUIC of each water iodine group, the iodine supply status of the WIC < 10 μg/L group, 10 μg/L ≤WIC ≤ 100 μg/L group, and WIC > 100 μg/L group was adequate, more than adequate, and excess, respectively.

The demographic characteristics of the different iodine supply groups are summarized in Table 2. The effective samples consisted of 260, 301, and 647 participants in the adequate iodine, more than adequate iodine, and excess iodine groups, respectively. Among the three groups, there was a statistically significant difference in the mean (± SD) values of age ($P = 0.001$) but not in BMI ($P = 0.822$). The proportion of gender did not differ significantly among the three groups ($P = 0.129$).

3.2. Influence of iodine supply on serum Tg levels as indicated by UIC in the three WIC groups

In total, 1208 salt samples were collected, and the coverage rates of non-iodized salt were 100%. The Tg levels differed significantly among the three groups ($P = 0.002$). The median serum Tg level in the excess iodine group [14.6 (9.0–23.5) μg/L] was significantly higher than those in the adequate iodine group [12.7 (8.3–19.2) μg/L] and the more than adequate iodine group [12.5 (7.7–18.3) μg/L] ($P = 0.042$ and $P = 0.004$), as shown in Table 3.

Comparisons of the prevalence of subjects with a Tg level greater than 40 μg/L showed the following results: significant differences between the adequate iodine group and the excess iodine group ($P < 0.001$); significant differences between the excess iodine group and the more than adequate iodine group ($P = 0.004$); but no significant difference between the adequate iodine group and the more than adequate iodine group ($P = 0.067$) (Table 3).

3.3. Frequency of thyroid diseases/thyroid function status with corresponding serum Tg values in the different iodine supply groups

For euthyroidism (Table 4), the prevalence of euthyroidism in the excess iodine group was lower than that in the adequate iodine group ($P = 0.001$) and the more than adequate iodine group ($P < 0.001$). No significant difference was found in Tg levels of euthyroid persons among the three groups ($P = 0.133$). For hypothyroidism, the prevalence in the excess iodine group was higher than that in the adequate iodine group ($P = 0.003$) and the more than adequate iodine group ($P = 0.001$). The Tg level of hypothyroid persons in the excess iodine group was significantly higher than that in the adequate iodine group ($P = 0.038$). There was no significant difference in Tg levels between the excess iodine group and the more than adequate iodine group ($P = 0.073$). For thyroid nodules, the occurrence differed significantly between the more than adequate iodine group and the excess iodine group ($P = 0.002$). However, the occurrence of thyroid nodules did not significantly differ between the adequate iodine group and the excess iodine group ($P = 0.028 > 0.0125$), and no significant difference was found in Tg levels of nodule persons among the three groups ($P = 0.841$). For TPOAb positivity, there were no significant differences in their prevalence among the three groups ($P = 0.095$), and no significant difference was found in Tg levels among the three groups ($P = 0.56$).

Table 1
Iodine status of different water iodine groups.

Water iodine group (μg/L)	N	WIC (μg/L) Median (interquartile)	UIC (μg/L) Median (interquartile)
< 10	260	7.4 (6.4, 8.4)	165.7 (112.6, 221.7)
10–100	301	83.5 (50.2, 92.8)	276.6 (190.0, 339.0)
> 100	647	263.5 (167.5, 352.6)	469.3 (345.1, 612.3)

Abbreviations: N, number; WIC, water iodine concentration; UIC, urinary iodine concentration.

3.4. Influence of thyroid diseases and other factors on serum Tg level

The serum Tg levels were significantly higher in subjects with hypothyroidism than in subjects with euthyroidism ($P < 0.001$) and in subjects with nodules than in subjects without nodules ($P < 0.001$) (Table 5). Moreover, the serum Tg level was significantly higher in subjects with a goitre than in subjects without a goitre ($P = 0.039$), and the serum Tg level was significantly lower in subjects with TPOAb positivity than in subjects with TPOAb negativity ($P = 0.004$). There was no significant difference between the serum Tg levels of subjects with hyperthyroidism and subjects with euthyroidism ($P = 0.658$).

The prevalence of elevated Tg was significantly higher in subjects with hypothyroidism than in subjects with euthyroidism ($P < 0.001$), in subjects with hyperthyroidism than in subjects with euthyroidism ($P = 0.002$), in subjects with nodules than in subjects without nodules ($P < 0.001$), and in subjects with a goitre than in subjects without a goitre ($P = 0.003$). The prevalence of elevated Tg did not differ significantly between subjects with TPOAb positivity and subjects with TPOAb negativity ($P = 0.127$).

The Tg level was significantly higher in women than in men [14.2 (8.8, 22.4) μg/L] vs. [11.3 (7.6, 18.6) μg/L, $P < 0.001$]. Spearman's rank correlation showed that age and TSH were positively related to Tg level (Age, r = 0.173, $P < 0.001$; TSH, r = 0.203, $P < 0.001$).

3.5. Relationship between Tg and iodine nutrition status indicated by MUIC and other factors

A multiple linear regression analysis was performed to determine the association between serum Tg level and iodine nutrition status indicated by MUIC and other factors (Table 6). After adjusting for age, sex, and BMI, it was found that the serum Tg level in the excess iodine group was significantly higher than that in the adequate iodine group ($\beta = 6.243$, $P = 0.01$). In addition, thyroid nodules ($\beta = 8.619$, $P < 0.001$), goitre ($\beta = 88.293$, $P < 0.001$) and hypothyroidism ($\beta = 9.876$, $P < 0.001$) were significantly related to the serum Tg level.

A logistic regression analysis was performed for the association between elevated Tg and iodine nutrition status indicated by MUIC and other factors (Table 7). Compared with those with adequate iodine intake, individuals with excess iodine intake had an increased risk of elevated Tg (OR= 4.565, $P = 0.001$). Similar to the results of the multiple linear regression analysis, the results of the logistic regression analysis showed that goitre (OR= 9.244, $P = 0.002$), thyroid nodules (OR= 2.315, $P < 0.001$) and hypothyroidism (OR=3.304, $P < 0.001$) were risk factors for elevated Tg. Elevated serum Tg was more likely present in individuals with hyperthyroidism. In addition, compared with subjects aged below 40, subjects aged above 40 had an increased risk of elevated Tg.

4. Discussion

In the present study, we analysed serum Tg distributions in subjects with different water iodine levels as well as the effects of thyroid diseases and other factors on serum Tg levels. As expected, the iodine supply status was different in different water iodine groups. The

Table 2
Characteristics of study participants in the different iodine supply groups.

Characteristics		Adequate Iodine group	More than adequate iodine group	Excess iodine group	$P^{※}$
Participants number		260	301	647	
Gender	Male/Female	64/196	96/205	174/473	0.129
Age (year)		44.9 ± 10.6	46.7 ± 10.1	47.7 ± 9.4	**0.001**
BMI (kg/m^2)		25.5 ± 3.9	25.5 ± 3.4	25.7 ± 3.9	0.822
Education level	Primary school	165	213	443	
	Junior high school	23	25	41	
	Senior high school	16	7	20	
	College	56	56	143	0.087
Marital status	Single or divorced	10	8	22	
	Married	250	293	625	0.723
Smoking	Yes	39	61	108	
	No	221	240	539	0.225
Alcohol consumption	Yes	35	45	77	
	No	225	256	570	0.416

Abbreviation: BMI, body mass index.
※: The χ^2 test was used for gender, education level, marital status, smoking, alcohol consumption and ANOVA test for age and BMI.

Table 3
Serum Tg level and frequency of elevated Tg in the different iodine supply groups.

Group	N	Tg (μg/L) Median (interquartile)	Elevated Tg # N (%)
Adequate iodine	260	12.7 (8.3, 19.2)[b]	6 (2.3)[a]
More than adequate iodine	301	12.5 (7.7, 18.3)[a]	16 (5.3)[a]
Excess iodine	647	14.6 (9.0, 23.5)	72 (11.1)

Abbreviation: N, number.
#: Tg> 40 μg/L.
[a]: Compared with the excess iodine group, $P < 0.01$.
[b]: Compared with the excess iodine group, $P < 0.05$.

increasing MUIC correlated with the increasing median WIC. However, the iodine status of the WIC < 10 μg/L group was not deficient, which may be due to the following reasons: (1) the areas selected in this study are closer to the sea, and high-iodine foods, e. g. sea fish and seaweeds, are easily obtained in these areas; (2) with changes in socioeconomic characteristics, eating out, consuming processed foods and packaged foods are becoming more popular. A study in China reported that the utilization rate of iodized salt in packaged foods is 88.46% [24]. Several studies have reported that iodine from household cooking salt does not play a critical role in the iodine status of residents living in coastal provinces in China [25,26]. The present findings demonstrated that the serum Tg level of the excess iodine group was substantially higher than that of the adequate iodine group, and multivariable regression analysis identified a significant association between the serum Tg concentration and excess iodine intake, which was consistent with previous studies [18,27]. The National Academy of Clinical Biochemistry (NACB) recommended that the upper reference limit for Tg is 40 μg/L in iodine-replete populations [22]. In the present study, the prevalence of elevated Tg ranged from 11.1% to 2.3% from the excess iodine group to the adequate iodine group. Similarly, in a study performed in primary schools in 12 countries, Zimmermann [28] reported that the frequency of elevated Tg values is significantly higher in both iodine deficiency and iodine excess, and they demonstrated that the prevalence of elevated Tg is less than 3% in the iodine sufficiency population.

We found that serum Tg levels were sensitive to abnormally high TSH values and that hypothyroidism was associated with higher Tg levels. Abnormally high TSH levels substantially affect the serum Tg level, as reported by Chong et al. [27], which corroborates the results of the present study. Serum Tg concentration increases due to TSH stimulation [29]. Furthermore, our results suggested that individuals with thyroid diseases, including thyroid nodules or goitre, had a higher Tg level than individuals without thyroid nodules or goitre, which was in line with previous studies [14,16,17]. Krejbjerg et al. reported that thyroid nodularity is associated with serum Tg [16], and Gao et al. suggested that thyroid nodules and goitres are risk factors for high serum Tg levels [17]. In addition, the present study demonstrated that the frequency of elevated Tg was significantly higher in the excess iodine group compared to the other groups and was significantly associated with thyroid diseases, including hypothyroidism, hyperthyroidism, nodules, and goitre. Although univariate analysis indicated that serum Tg levels in women were higher than those in men, the difference was not significant in the multivariate analysis. In addition to iodine nutrition status and thyroid diseases, age plays an important role in serum Tg levels. In the present study, age was positively associated with serum Tg levels, which was similar to the results reported by Chong et al. [27].

The present study also indicated that excess iodine intake may lead

Table 4
Frequency of thyroid diseases/thyroid function status with corresponding serum Tg values in the different iodine supply groups.

Factors	Adequate iodine		More than adequate iodine		Excess iodine		$P^{★}$	Total	
	(N = 260)		(N = 301)		(N = 647)			(N = 1208)	
	N (%)	Tg※ (μg/L)	N (%)	Tg※ (μg/L)	N (%)	Tg※ (μg/L)		N (%)	Tg※ (μg/L)
Euthyroidism	233 (89.6)[a]	12.7 (8.4, 19.1)	272 (90.4)[a]	12.4 (7.7, 17.6)	522 (80.7)	13.3 (8.3, 20.7)	0.133	1027 (85.0)	12.9 (8.2, 19.5)
Hypothyroidism	26 (10.0)[a]	15.0 (7.4, 22.7)[b]	29 (9.6)[a]	18.2 (6.5, 23.8)	115 (17.8)	21.7 (12.4, 40.0)	**0.009**	170 (14.1)	19.3 (10.9, 31.9)
Hyperthyroidism	1 (0.4)	11.5	0	-	10 (1.5)	15.8 (5.0, 54.4)	-	11 (0.9)	14.0 (5.7, 48.7)
Thyroid nodules	51 (19.6)	18.2 (10.7, 27.9)	53 (17.6)[a]	14.2 (11.0, 26.8)	172 (26.6)	16.9 (9.8, 27.4)	0.841	276 (22.8)	16.2 (10.2, 27.2)
Goitre	2 (0.8)	11.6	3 (1.0)	24.1	4 (0.6)	248.0 (55.9, 309.6)	-	9 (0.7)	24.1 (10.6, 248.0)
TPOAb positivity	7 (2.7)	5.0 (1.9, 17.8)	13 (4.3)	11.9 (2.1, 18.2)	39 (6.0)	9.5 (3.3, 20.5)	0.56	59 (4.9)	9.5 (2.5, 20.5)

Abbreviation: N, number.
※: Tg was shown as median (interquartile) or median.
★: The Kruskal–Wallis test was used for euthyroidism, hypothyroidism, thyroid nodules, and TPOAb positivity.
[a]: Compared with the excess iodine group, $P < 0.01$.
[b]: Compared with the excess iodine group, $P < 0.05$.

Table 5
Serum Tg level in different thyroid diseases.

Thyroid disease		N	Tg (μg/L) Median (interquartile)	$P^{※}$	Elevated Tg[#] N (%)	$P^{△}$
Hypothyroidism	Yes	170	19.3 (10.9, 31.9)		33 (19.4)	
	No (euthyroidism[&])	1027	12.9 (8.2, 19.5)	**< 0.001**	58 (5.6)	**< 0.001**
Hyperthyroidism	Yes	11	14.0 (5.7, 48.7)		3 (27.3)	
	No (euthyroidism[&])	1027	12.9 (8.2, 19.5)	0.658	58 (5.6)	**0.002**
Thyroid nodules	Yes	276	16.2 (10.2, 27.2)		38 (13.8)	
	No	932	12.9 (7.8, 19.5)	**< 0.001**	56 (6.0)	**< 0.001**
Goitre	Yes	9	24.1 (10.6, 248.0)		4 (44.4)	
	No	1199	13.4 (8.3, 21.1)	**0.039**	90 (7.5)	**0.003**
TPOAb positivity	Yes	59	9.5 (2.5, 20.5)		8 (13.6)	
	No	1149	13.5 (8.7, 21.3)	**0.004**	86 (7.5)	0.127

Abbreviation: N, number.
[&]:0.27 μIU/mL≤ TSH≤ 4.20 μIU/mL.
[※]: The Mann–Whitney U test was used for hypothyroidism, hyperthyroidism, thyroid nodules, goitre and TPOAb positivity.
[△]: The χ^2 test was used for hypothyroidism, hyperthyroidism, thyroid nodules, goitre and TPOAb positivity.
[#]: Tg> 40 μg/L.

Table 6
Multiple linear regression analysis for clarifying the determining factors of serum Tg level.

Variables	β[#]	95% CI	*P*
Male vs. female	-6.011	-12.732, 0.709	0.08
Age	0.244	0.048, 0.439	**0.015**
BMI	0.155	-0.350, 0.659	0.548
Hypothyroidism vs. without hypothyroidism	9.876	4.496, 15.256	**< 0.001**
Goitre vs. without goitre	88.293	66.855, 109.732	**< 0.001**
Nodules vs. without nodules	8.619	4.137, 13.101	**< 0.001**
TPOAb positivity vs. TPOAb negativity	3.791	-4.821, 12.403	0.388
Smoking vs. without smoking	-0.577	-7.431, 6.276	0.869
Drinking vs. without drinking	2.433	-4.646, 9.512	0.50
More than adequate iodine vs. adequate iodine	3.516	-1.922, 8.953	0.205
Excess iodine vs. adequate iodine	6.243	1.485, 11.002	**0.01**

Abbreviations: BMI, body mass index; CI, confidence interval.
[#]: Regression coefficient.

Table 7
Logistic regression analysis for clarifying the determining factors of elevated Tg[#].

Variables		OR	95% CI	*P*
Age	≤ 40	Reference		
	> 40	3.575	1.673, 7.642	**0.001**
Gender	Male	0.347	0.113, 1.063	0.064
	Female	Reference		
Hypothyroidism	Yes	3.304	2.009, 5.434	**< 0.001**
	No	Reference		
Hyperthyroidism	Yes	6.425	1.525, 27.075	**0.011**
	No	Reference		
Nodules	Yes	2.315	1.445, 3.71	**< 0.001**
	No	Reference		
Goitre	Yes	9.244	2.212, 38.636	**0.002**
	No	Reference		
Iodine group	Adequate	Reference		
	More than adequate	2.572	0.953, 6.94	0.062
	Excess	4.565	1.903, 10.947	**0.001**
Smoking	Yes	0.558	0.194, 1.608	0.280
	No	Reference		
Drinking	Yes	3.266	0.967, 11.029	0.057
	No	Reference		

Abbreviations: OR, odds ratio; CI, confidence interval.
[#]: Tg> 40 μg/L.

to a high prevalence of thyroid nodules and hypothyroidism, which was similar to previous studies [3,30,31]. Iodine is an external environmental factor, and it is a direct factor that affects serum Tg levels and the prevalence of thyroid diseases. Interestingly, the Tg level of hypothyroidism in the excess iodine group was higher than that in the adequate iodine group, but there were no significant differences in the Tg levels of euthyroidism among the three iodine groups. This finding indicated that there may be an interaction effect between excess iodine intake and elevated TSH on Tg levels. No interaction effect was observed between excess iodine intake and other thyroid diseases on serum Tg level. The univariate analysis indicated that the serum Tg level was significantly associated with multiple factors, including iodine intake, thyroid diseases, age, and sex. However, the prevalence of thyroid diseases was also affected by iodine intake. Multivariable regression analysis was used to exclude the potential influence of confounders. After controlling for the effects of other related factors, excess iodine intake was demonstrated to substantially affect serum Tg levels in adults.

The strength of the present study was that the survey villages supplied with non-iodized table salt were selected to avoid the influence of iodized salt. In these areas, high iodine intake is mainly due to high iodine water intake rather than iodized salt intake. Furthermore, when an immunometric assay is used to test Tg, a subject with TgAb positivity will most likely have a lower Tg value [22,29]. To avoid the effects of TgAb positivity on serum Tg measurement, participants with TgAb positivity were excluded in the present study. Nevertheless, the present study also had limitations. First, a dietary investigation regarding food iodine was not conducted. Second, the proportion of gender was not balanced among the three different iodine supply groups, which may be attributed to a large proportion of rural men working in cities with the women staying in their hometowns in China. Despite this imbalance, there was no significant difference in the distribution of sex among the three groups. In addition, as a cross-sectional survey, this study was not able to unveil the mechanisms involved in the observed phenomena.

Currently, IDD has been controlled and is in a state of sustainable elimination in China, and the iodine nutrition status is sufficient in most areas, except high water iodine areas. The most recent study has reported that the iodine nutrition status of people living in high water iodine areas is still in excess, leading to a high prevalence of thyroid diseases [10]. In addition to urinary iodine, a sensitive indicator of excess iodine intake is required. We confirmed that high levels of serum Tg and a high frequency of elevated Tg were significantly associated with excess iodine intake, suggesting that Tg may be utilized as a biomarker of excess iodine intake.

5. Conclusions

In summary, serum Tg level can be a promising biomarker of

excessive iodine intake. Multiple factors, especially the presence of thyroid diseases, are associated with Tg. This should be taken into consideration when using Tg as a biomarker of excessive iodine intake in an adult population.

Consent for publication

All authors consent for publication.

Authors' contributions

Sun D and Liu P contributed to the study's conception and design. Material preparation and data collection were performed by Zhang W, Yao J, Meng F, Fan L, Li M, Liu L, Jiang W and Lv C. Data analysis was performed by Du Y. The first draft of the manuscript was written by Du Y. All authors commented on previous versions of the manuscript.

Funding

This study was supported by grants from the National Natural Science Foundation of China (81830098) and the Natural Science Foundation of Heilongjiang Province (TD2019H001).

Ethical statement

Research approval was obtained from the Ethics Committee of Harbin Medical University. The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Data Availability

The datasets generated during the current study are not publicly available due to privacy considerations but are available from the corresponding author at a reasonable request.

Acknowledgements

We thank all the organizations that participated in this survey: the Centers for Endemic Disease Control in Shandong and the residents who participated in this survey.

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