Potential role of iodine excess in papillary thyroid cancer and benign thyroid tumor: A case–control study

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Running title: Excessive iodine affects TgAb in thyroid cancer?

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ABSTRACT

Background and Objectives: The relationship between nutritional status of iodine and thyroid tumor is unclear. We investigated the association between urinary iodine concentration and thyroid function in patients with papillary thyroid cancer, benign thyroid tumor and healthy individuals. **Methods and Study Design:** We compared the biomarkers of thyroid function and urinary iodine concentration within and between each group. A regression analysis was used to identify risk factors for papillary thyroid cancer. Correlation analysis was performed to determine whether any significant correlation exists between urinary iodine concentration and thyroid function biomarkers. **Results:** The iodine nutrition statuses of these three groups were adequate (median urinary iodine concentration=100–199 μg/L). However, the median urinary iodine concentration of papillary thyroid cancer (174.7 μg/L) and benign thyroid tumor (165.04 μg/L) groups was significantly higher than that of the healthy control group (135.8 μg/L) (p<0.05). The regression analysis showed that thyroglobulin antibody was an independent risk factor for papillary thyroid cancer. After adjusting for age and gender, the association between thyroglobulin antibody and urinary iodine concentration was significant (β: 0.002; p<0.05). In subgroup analyses, significant correlations was noted only in the papillary thyroid cancer group (adjusted β: 0.002; 95% confidence interval: 0.000–0.003). **Conclusions:** Excessive iodine in patients with thyroid tumors may affect thyroglobulin antibody, which may be an independent risk factor for papillary thyroid cancer.

Key Words: thyroid cancer, papillary thyroid cancer, urinary iodine concentrations, Nanjing, thyroglobulin antibody

INTRODUCTION

The incidence rate of thyroid cancer (TC), the most common endocrine malignancy, has been steadily increasing over the past few decades, predominantly in women.[1] According to the 2008–2012 China Cancer Registry Annual Report, the crude incidence of TC was 7.56/100,000, ranking the seventh in terms of cancer incidence rates.[2-3] Papillary thyroid cancer (PTC) is the most common pathological type of TC, accounting for more than 80% of the total TC incidence.[4] Exposure to radiation when young; a family history of TC or thyroid disorders, obesity, and metabolic syndrome; environmental pollutants; or iodine intake are potential risk factors for PTC.[5-7]

Iodine is a necessary trace element for the human body. The association between iodine intake and PTC is uncertain,[8-12] although abnormal iodine nutritional status is clearly a primary determinant of benign thyroid disorders, such as hyperthyroidism or hypothyroidism.[13] Furthermore, TC has relatively increased in China, where the annual incidence of TC in the high iodine area of Hebei (median urinary iodine concentration [UIC]: 651μg/ L) was 19.37/100,000, which is significantly higher than that in overall China (7.56/100,000), and pathological results confirmed these cases as PTC.[14] Nanjing, Jiangsu Province, is located in the lower reaches of Yangtze River. According to the National Survey Report on Iodine Content in Drinking Water of the National Health Commission of China in 2019, Nanjing belongs the iodine-deficient area (water iodine content <10 μg/L), but the only regional study on iodine nutrition is limited to pregnant women or school-aged children,[15,16] which have reported that the median UIC was 196.7 μg/L in pregnant women and 152.0 μg/L in lactating women.[16]

Considering that no relevant clinical relationship exists between thyroid tumors and urinary iodine levels in Nanjing, we investigated the iodine nutrition status and thyroid function of patients with PTC or benign thyroid tumor (BTT) and analyzed the association between UIC and thyroid function. We surmised this would provide the needed data to identify treatment strategies or to safeguard public health.

MATERIALS AND METHODS

Study population

The study was approved by the Institutional Review Board of the Second Affiliated Hospital of Nanjing Medical University (2015KY042). Written informed consent was obtained from all adult subjects.

Patients with initial-onset PTC or BTT were recruited from the endocrine surgery department of the Second Affiliated Hospital of Nanjing Medical University from January 2017 to March 2019. According to the results of the postoperative pathological examination, patients were classified into two groups: a PTC group and a BTT group. A total of 90 staff members who had visited the medical examination center for physical examinations in October 2018 were recruited. These individuals were from a company in Nanjing. Furthermore, a healthy control (HC) group was created consisting of people with normal thyroid function. We recruited only those individuals who lived in Nanjing for more than 5 years and did not have a history of thyroid surgery or iodine treatment (such as using an iodine contrast agent or taking iodine-containing drugs). They were living in Nanjing for 2

weeks before the study, without consuming drugs that affect thyroid function, iodine nutrition, or iodine-rich food in excessive amounts.

Data acquisition

The hospital electronic medical records were used to obtain information regarding the PTC group, including age, sex, operational records, and postoperative pathological reports.

In population studies, for assessing and monitoring the iodine nutrition status, the best method is determining the median UIC in random spot urine samples in microgram per liter.9 A total of 10 mL of fasting urine was collected from 6:00 to 8:00 for the quantitative detection of urine iodine. For the PTC and benign thyroid groups, fasting urine was obtained preoperatively. UIC was determined according to the Sandell–Kolthoff reaction after ammonium persulfate treatment.

In this study, we regarded median UIC <99 μg/L as iodine deficiency, 100–199 μg/L as adequate iodine nutrition, 200–299 μg/L as more-than-required iodine intake, and >300 μg/L as excess iodine intake as per the guidelines of World Health Organization (WHO).[17] Preoperative serum thyroid stimulating hormone (TSH), total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4), thyroglobulin antibody (TgAb), and thyroperoxidase antibody (TPOAb) were tested using chemiluminescence detection kits from Roche at the Laboratory Medicine Center of our hospital following manufacturer's instructions.

Statistical analyses

Data processing was performed using SPSS 20.0 statistical software. The Shapiro–Wilk test was used to demonstrate the normality of distribution for all variables, after which the Mann–Whitney U test, Mood's median tests, or Student's t-test was applied accordingly to each variable. Values were presented as the median (1st quartile, 3rd quartile) [M (Q1,Q3)] for continuous variables and as numbers and percentages (%) for categorical variables. The Kruskal–Wallis Rank Sum test and chi-square test were used to discuss differences in clinical measurements. A Spearman's rank-based correlation analysis was performed to assess whether any significant correlation exists between urine iodine levels and TgAb. A p value of <0.05 was regarded statistically significant.

RESULTS

Participant characteristics

After excluding cases with incomplete data or insufficient sample size, 221 patients with PTC were enrolled, including 58 men and 163 women, aged 19–79 years. The median (Q1, Q3) age was 43 (35, 54.5) years. A total of 203 patients with BTTs, including thyroid adenomas and thyroid nodules, were enrolled, aged 17–78 years. The median (Q1, Q3) age was 55 (46, 63) years. We enrolled 82 healthy controls, including 15 men and 67 women, aged 23–60 years, with a median (Q1, Q3) age of 41 (38, 49) years. The characteristics of patients and healthy controls are summarized in Table 1.

High iodine levels in urine of patients with benign thyroid and PTC

The iodine nutrition status of the three groups was iodine adequate (median UIC: 100–199 μg/L). Results showed that the median UICs were significantly higher in the PTC (174.7 μg/L) and BTT (165.04 μg/L) groups than in the healthy control group (135.8 μg/L) (p<0.05).

The iodine insufficiency rates (urinary iodine <100 μg/L) of both the groups (10.28% [22 of 214 patients] in the PTC group and 9.37% [18 of 192 patients] in the BTT group) were similar (Table 2) but were higher than the iodine insufficiency rate of the HC group (3.65% [3 of 82 patients]). Moreover, the iodine excess rate (urinary iodine ≥300 ug/L) of the PTC group (19.62%, as compared with 9.37% in the BTT group) was higher than that of the HC group (6.09%; Table 2).

Comparison of thyroid function in patients with benign and malignant thyroid tumors and healthy controls

As summarized in Table 1, no significant differences were observed among the three groups (PTC, BTT, and HC groups) with respect to FT4 and T3. However, FT3 and T4 levels in patients with PTC and benign thyroid mass were significantly higher than did those in the healthy control group. The TgAb positivity rate (TgAb >115 IU/mL) was higher in the PTC group (22.6%) than in the BTT group (10.2%) and also than in the HC group (2.5%; Table 1). Thirty-seven TPOAb positivity (TPOAb >34 IU/mL) events (17.8%) occurred in the PTC group, which was significantly higher than in the other groups. On the basis of a logistic regression multivariable analysis adjusting for T3, T4, TSH, FT3, FT4, TgAb, TPOAb, age, sex, and urine iodine, only TgAb was an independent risk factor for PTC (p=0.018).

Association of TgAb with urine iodine and its prediction for PTC

We further analyzed the effect of urinary iodine on TgAb Spearman's rank-based correlation analysis revealed that the correlation was not significant (r=0.054, p=0.248). Because the distribution of thyroid antibodies presents a skewed distribution, the logarithmic approximation to normal was used for analysis. Pearson general correlation analysis was used (r=0.156, p<0.001). Then, a linear model was used, where the result was significant (β=0.002), and after adjusting for age and gender, the result continued to be significant (β=0.00176, p=0.000559). In subgroup analyses, TgAb levels were positively correlated to the urinary iodine index in the PTC group after adjusting for age and gender (adjusted β=0.002; 95% confidence interval=0.001–0.003; Table 3, online only). However, no significant correlations were observed in the other two groups (Table 3).

DISCUSSION

Iodine is an essential trace element of the human body and the necessary raw material for the synthesis of thyroid hormones. It plays an essential role in maintaining health. The global strategy of correcting iodine deficiency through universal salt iodization has remarkably improved the population health in China.[16] However, a U-shaped curve shows a relationship between iodine status and thyroid disease. Both deficient and excessive iodine intake may induce thyroid dysfunction.[18-19]

The recommended daily iodine intake by WHO/UNICEF/ICCIDD is 120 μg for children, 150 μg for adolescents or adults, and 250 μg for pregnant or lactating women. In healthy, iodine-replete adults, >90% of the dietary iodine is absorbed from the small intestine and >90% is excreted within 24−48 hours. The use of spot urine collections to measure the UIC (expressed as the median in μg/L) was recommend to assess iodine intake and status of populations by the WHO.[17,20] Because the median UIC reflects consumption from all dietary sources, it is a useful biomarker of recent exposure to iodine in populations.[17] Usually, iodine deficiency occurs when the median UIC is <100 μg/L.[20]

In this context, our results showed that median UICs in PTC, BTT, and HC groups were 174.7, 165.04, and 135.8 μg/L, respectively. The median UIC and iodine nutrition status in these three groups were similar to other reports in Nanjing.[21-22] All were within the sufficient range of iodine recommended by WHO/UNICEF/ICCIDD. Paradoxically, the iodine insufficiency rate (urinary iodine <100 μg/L) and iodine excessive rate (urinary iodine ≥300 μg/L) of the PTC group were higher than did those of the HC group (Table 1). Of note, the iodine excess rate (urinary iodine ≥300 μg/L) of the PTC group (19.62%) was higher than that

of the BTT group (9.37%). These data suggested that the iodine nutrition status of TC patients in this area is excessive compared with that of the general population.

Although animal studies have shown that iodine deficiency is a promoter of thyroid carcinogenesis rather than an initiator, iodine excess may also act as a weak promoter for TC.[9,23-24] The relation of thyroid tumors produced in these animal experiments to human lesions has never been satisfactorily explained. A large cross-sectional study found no correlation between iodine status and TC prevalence in a coastal region of China.[25] A recent meta-analysis study based on data from 22 case–control studies showed that high iodine intake was not a risk factor for PTC, and elevated urinary iodine was only a specific characteristic of the disease.[26] Our study applied a logistic regression multivariable analysis adjusting for T3, T4, TSH, FT3, FT4, TPOAb, age, sex, and urine iodine, which showed that TgAb was an independent risk factor for PTC but high iodine intake was not. Thus, whether changes in iodine intake contribute to PTC remains controversial.

Analysis of our data showed that TgAb and TPOAb positivity occurred at higher rates in the PTC group than in both the BTT and HC groups (22.6% vs 10.2% and 22.6% vs 2.5%, respectively, for TgAb; 17.8% vs 10.7% and 17.8% vs 3.7%, respectively, for TPOAb). However, further analysis showed that only TgAb levels were positively correlated with the urinary iodine index. In subgroup analysis, the correlation was found to be significant only in the PTC group after adjustments for age and sex. TgAb has several different antigenic domains (epitopes) for antibody binding.[27] In patients with autoimmune diseases, TgAb recognition is usually limited to some areas of the TG molecule.[27] Thyroid peroxidase (TPO) is crucial in the synthesis of thyroid hormones. It exists on the cell membrane at the top of the thyroid follicular cell.28 High-dose iodine can cause oxidative stress to release excessive H_2O_2,[29] which damages thyroid cells. Iodine can directly or indirectly increase the number of CD4+/CD8+ T cells to increase the levels of TgAb production and of TPO antibodies.[30,31]

Furthermore, studies have stated that iodine intake might be more closely related to changes in thyroglobulin antibody levels.[31-34] Rose et al.[34] reported that more highly iodinated Tg may be more antigenic and thus result in higher TgAb levels, providing an explanation of the association with higher UICs. In susceptible individuals, excessive increases in iodine exposure or intake can alter the spatial structure directly or through active oxygen-mediated proteolysis.[35] Moreover, thyroid epithelial cell damage can result, causing the release of self-antigen molecules into the blood together with cytokines such as interleukin-1 and interleukin-8, thereby promoting autoimmune reaction and increasing the immunogenicity of TgAb.[36]

Thyroid hormones are direct indicators of thyroid function but not generally used to assess iodine status. The respective values are usually within the normal range during mild-to-moderate changes in iodine levels.[37] Our results suggest that the median levels of FT3 and T4 in the PTC and BTT populations were higher than those in the HC group. We cannot eliminate the possibility of confusion caused by the smaller number of members in the HC subgroup.

Overall, we speculate that excessive iodine intake may promote the occurrence and development of thyroid autoimmunity. Continual stimulation of antithyroid antibody might also increase the risk of thyroid damage and subsequent malignancy (such as PTC).

The limitations of the current study mainly arise from the cross-sectional study design that cannot warrant a causal relationship between iodine nutritional status and TC. Additionally, we included patients with different disease stages, and the analysis was not powered to the pathological features of tumors in the PTC group. Moreover, all data were obtained from our hospital. Thus, the results were not universal. Despite the limitations, this study would be useful for safeguarding public health. Therefore, it underscores the importance of additional studies with more patients to determine the clinical implications of these correlations.

Conclusion

In conclusion, our data demonstrate a difference in iodine statuses between the PTC group (or BTT group) and the healthy cohort. The iodine excess (urinary iodine ≥ 300 μg/L) rate in the PTC group was higher than that in the BTT group and the HC group, although the logistic regression multivariable analysis failed to reach statistical significance considering UIC as a risk factor for PTC. TgAb was an independent risk factor for PTC, and excessive iodine in patients with thyroid tumors may affect TgAb. However, the associations were weak and inconsistent, and iodine intake was not a risk factor for PTC, and high urinary iodine was only a specific characteristic of the disease. Prospective data and other biomarkers of iodine status must be collected from the cohort that measures the total amount of iodine exposure.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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Table 1. Characteristics of the participants

Characteristic	PTC group (N=221)	BTT group (N=203)	Healthy control group (N=82)
Age at diagnosis year	43 (35, 54.5)	55 (46, 63)	41 (38, 49)
Gender -no. (%)			
Male	58 (26%)	47 (23%)	15 (18%)
Female	163 (74%)	156 (77%)	67 (82%)
BMI -kg/m^2	23.66 (21.45, 25.39)	23.42 (21.72, 25.22)	24.27 (22.25, 26.11)
AHI -no. (%)			
≤50 thousand Yuan	36 (16.3%)	29 (14.3%)	12 (20.8%)
50~99 thousand Yuan	139 (62.9%)	117 (57.6%)	44 (28.1%)
≥ 00 thousand Yuan	46 (20.8%)	57 (28.1%	26 (31.7%)
Level of education -no. (%)			
Junior	44 (19.9%)	51 (25.1%)	20 (24.4%)
Senior	97 (43.9%)	86 (42.4%)	28 (34.1%)
University	80 (36.2%)	66 (32.5%)	34 (41.5%)
Smoking Status -no. (%)			
Never	185 (83.7%)	160 (78.8%)	69 (84.1%)
Former	13 (5.9%)	18 (8.9%)	5 (6.1%)
Current	23 (10.4%)	25 (12.3%)	8 (9.8%)
Current Drinking -no. (%)	38 (17.2%)	44 (21.7%)	11 (13.4%)
FT3 -pmol/L	4.91 (4.49, 5.39)[§]	4.92 (4.57, 5.37)[§]	4.44 (3.97, 5.10)
FT4 -pmol/L	17.55 (16.05, 19.44)	17.20 (15.12, 18.94)	17.32 (15.74, 18.79)
T3 -nmol/L	1.81 (1.57, 2.01)	1.78 (1.62, 2.09)	1.89 (1.66, 2.18)
T4 -nmol/L	104.00 (93.2, 118.5)[§]	104.5 (92.6, 116.7)[§]	93.85 (87.18, 109.07)
TSH - μ IU/ml	1.97 (1.23, 2.92)	1.75 (1.03, 2.78)	1.79 (1.18, 2.26)
TgAb (+)[†] -no.(%)	47 (22.6%)[§¶]	19 (10.2%)	2 (2.5%)
TPOAb (+)[‡] -no.(%)	37 (17.8%)[§]	20 (10.7%)	3 (3.7%)
UIC			
Minimum	50	53.46	85.6
P_{25}	134.3	129.58	120.2
Median	174.7§	165.04[§]	135.8
P_{75}	217.8	213.9	162.3
Maximum	600.0	600.0	241.8

PTC: papillary thyroid cancer; BTT: benign thyroid tumor; BMI: body mass index; AHI: annual household income FT3: free triiodothyronine; FT4: free thyroxine; T3: total triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone; TgAb: thyroglobulin antibody; TPOAb: thyroperoxidase antibody; UIC: urinary iodine concentration.
Data are presented as medians (interquartile ranges) for the non-normally distributed variables.
[†]TgAb (+)：negative (TgAb <115 IU/mL) and positive (TgAb ≥ 115 IU/mL).
[‡]TPOAb (+): negative (TPOAb <34 IU/mL) and positive (TPOAb ≥ 34 IU/mL).
[§]p<0.05, statistical difference compared with the HC group.
[¶]p<0.05, statistical difference compared with the BTT group

Table 2. Urinary iodine concentration of the participants (μg/L)

	Distribution of iodine nutritional status in different groups				Number of patients (N)
	<100 μg/L (%)	100~199 μg/L (%)	200~300μg/L (%)	>300 μg/L (%)	
HC group	3 (3.65)	68(89.02)	6 (7.31)	5 (6.09)	82
BTT group	18 (9.37)	114 (59.37)	42 (21.87)	18 (9.37)	192
PTC group	22 (10.28)	108 (50.46)	42 (19.62)	42 (19.62)	214

Table 3. β (95% CI) of groups according to the correlation between TgAb level and urinary iodine index

	β-Coefficient (95% *CI*)	*p*-value	β-Coefficient (95% *CI*) (after adjustment for age and gender)	*p* value (after adjustment for age and gender)
HC group	0.002 (-0.001,0.005)	0.116	0.002 (-0.000,0.005)	0.121
BTT group	-8.63e-05 (-0.002,0.001)	0.921	5.26e-05 (-0.001,0.002)	0.952
PTC group	0.002(0.000,0.003)	0.028	0.002 (0.000,0.003)	0.025