Association of Excess Dietary Iodine Intake with Papillary Thyroid Carcinoma

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid carcinoma and accounts for 70–80% of all thyroid carcinomas. After the global iodine fortification of salt and food, the incidence of PTC has been increasing throughout the world in recent years.

Aims: To determine the relationship between excessive dietary iodine intake and PTC.

Patients and methods: This cross-sectional study was carried out at the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Dhaka, from March 2020 to June 2021. A total of 111 patients were included in this study, of whom 53 were pre-operative papillary thyroid carcinoma patients and the rest, 58, were age- and sex-matched healthy individuals. Their urinary iodine concentrations were measured in the laboratory of the Bangladesh Reference Institute for Chemical Measurements (BRICM). Urinary iodine concentration is a good marker of dietary iodine intake. Statistical analysis of the results was obtained using Windows-based computer software devised with Statistical Packages for Social Sciences (SPSS) version 23.0.

Results: The mean urinary iodine concentration was 223.54±55.78 microgram/liter in the PTC group and 154.29±61.83 microgram/liter in the healthy group. A remarkable number of participants in both the PTC group 42 out of 53 (79.3%) and the healthy group 18 out of 58 (31.0%) had biochemical evidence of excess iodine intake. Excess iodine intake significantly ($p<0.05$) increased with 8.48 times odds (95% CI 3.30-22.33) in PTC patients.

Conclusion: This study revealed that a significant number of participants in the PTC group had evidence of excess iodine intake compared to that of the healthy group, which suggests that excess dietary iodine intake may be related to the occurrence of PTC.

Keywords: Papillary Thyroid Cancer, Dietary iodine intake, Urinary iodine concentration.

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INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignancy, and incidence rates have been steadily increasing in most countries over the last few decades, particularly in women (1). Comparing populations around the world, there is a greater than ten-fold difference in incidence; high incidence areas (incidence rates greater than 10 per 100,000 women) are Japan and the Pacific Islands, Italy, and several countries in the Americas. Incidence rates in developed countries are more than twofold higher than in developing countries (in women, 11.1/100,000 versus 4.7/100,000) (2). If such trends continue, thyroid cancer will be the fourth most common cancer in the U.S. by 2030 (3). Papillary thyroid cancer (PTC) is by far the most prevalent subtype in most countries, accounting for greater than 80 percent of thyroid cancer, but anaplastic thyroid cancer (ATC), because of its poor prognosis, accounts for a large portion of the mortality. Increased screening and diagnostic testing are likely the major, but may not be the only, contributors to the rising incidence of thyroid cancer (4, 5). Suspected risk factors include radiation exposure during childhood (whether from nuclear accidents, natural radiation, or medical imaging) (6); obesity and the metabolic syndrome (7, 8); environmental pollutants (9); a family history of thyroid cancer or thyroid disorders; and possibly iodine intake (1).

During these decades of increasing iodine intake worldwide, population studies have demonstrated a significant rise in the incidence of thyroid cancer (10). Gharib (11) reported that increasing iodine intake seems to result in less aggressive thyroid cancers like papillary thyroid carcinoma (PTC), whereas iodine deficiency is associated with more aggressive forms such as follicular and anaplastic cancers in the general population.

Dietary iodine intake might also be a risk factor for thyroid cancer (12). Iodine is an essential micronutrient and a vital component of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), that are involved in various biochemical and metabolic pathways throughout the human body (13). Thyroid hormones maintain homeostasis through the thyroid function feedback loop between the hypothalamus-pituitary axis and the thyroid gland. Even if there is a temporary excess or insufficient intake of iodine, thyroid hormones are in a balanced state. However, both chronic iodine deficiency and excess can lead to thyroid dysfunction by interfering with homeostasis (12, 14).

This study is aimed at evaluating the association of excess dietary iodine intake with PTC.

PATIENTS AND METHODS

This cross-sectional study was carried out at the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Dhaka, from March 2020 to June 2021 as part of the fulfillment of an MD degree in nuclear medicine (residency). A total of 53 FNAC- or biopsy-proven PTC patients from different areas of Bangladesh waiting for surgery were enrolled in this study. On the other hand, 58 age- and sex-matched healthy individuals were included in a comparison group. The total number of participants was 111. Patients with known renal disease, patients recently treated with Lugol's iodine, or patients who have undergone investigations using iodinated contrast media were excluded from the study. The research work was approved by the Scientific Review Committee (SRC) and Medical Research Ethics Committee (MREC) of NINMAS, and proper permission was obtained from the institutions and departments concerned for this study. Informed written consents were taken from all the participants. Confidentiality was strictly maintained, and participants had the freedom to withdraw themselves from the study at any time.

Personal information, clinical history, physical examination, an ultrasonogram of the thyroid gland, and the serum thyroid stimulating hormone (TSH) level of each participant were collected. Urinary iodine concentrations were measured in the laboratory of the Bangladesh Reference Institute for Chemical Measurements (BRICM). Urinary iodine concentration is a good marker of dietary iodine intake. Age, sex, body weight, home district, frequency of intake of seafood, commercial brand of dietary iodized salt, and socio-economic condition were independent variables, and urinary iodine concentration was a dependent variable of this study. All findings were collected on a pre-designed data collection sheet. Iodine nutrition status was assessed according to the urinary iodine concentration recommended by the World Health Organization (WHO).

STATISTICAL ANALYSIS

Statistical analyses were carried out using the Statistical Package for Social Sciences, version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The unpaired t-test was used to test quantitative variables that were presented as means and standard deviations. The quantitative observations were represented by frequencies and percentages, and they were analyzed using the Chi-Square test, as shown in the cross-tabulation. An odds ratio with a 95% confidence interval (CI) was performed, and $P < 0.05$ was considered a statistically significant difference.

RESULTS

The mean age was 38.09±15.52 years in the PTC group and 37.74±16.78 years in the healthy control group. Female participants in the PTC and healthy comparison groups were found to be 38 (71.7%) and 43 (74.1%), respectively. The mean body weight was 64.66±10.12 kilograms in the PTC group and 63.55±12.42 kilograms in the healthy group. The difference was not statistically significant ($p > 0.05$) between the two groups.

Table 1 shows the distribution of the study subjects according to their iodine nutrition status based on urinary iodine concentrations recommended by the WHO. It was observed that 73.6% of patients had biochemical evidence of mild iodine excess, and 5.7% of patients had evidence of iodine excess with a risk of adverse health consequences in the PTC group. On the other hand, 31.0% of individuals had evidence of mild iodine excess, and no one (0%) had evidence of marked

iodine excess in the healthy group. The mean urinary iodine concentration was 223.54±55.78 microgram/liter in the PTC group and 154.29±61.83 microgram/liter in the healthy group. The difference between the two groups was statistically significant (p 0.05).

Table 1: Distribution of the study subjects according to iodine nutrition status on the basis of urinary iodine concentration recommended by WHO (n=111)

Iodine nutrition status represented by urinary iodine concentration in microgram/liter (µg/l)	PTC patients (n=53)		Healthy volunteers (n=58)	
	n	%	n	%
Severe iodine deficiency (Urinary iodine concentration <20 µg/l)	0	0	1	1.7
Moderate iodine deficiency (Urinary iodine concentration 20-49 µg/l)	0	0	5	8.6
Mild iodine deficiency (Urinary iodine concentration 50-99 µg/l)	3	5.7	6	10.3
Adequate/ normal iodine nutrition (Urinary iodine concentration 100-199 µg/l)	8	15.1	28	48.3
Mild iodine excess (Urinary iodine concentration 200-299 µg/)	39	73.6	18	31.0
Iodine excess with risk of adverse health consequences (Urinary iodine concentration ≥300 µg/l)	3	5.7	0	0

Table 2 shows the distribution of the study subjects according to the presence or absence of high iodine intake. It was observed that the majority (79.3%) of patients had biochemical evidence of excess iodine intake in the PTC group as their urinary iodine concentrations were 200 microgram/liter or above. On the other hand, only 31.0% of individuals had biochemical evidence of excess iodine intake in the healthy group. Excess iodine intake significantly (p < 0.05) increased with 8.48 times odds (95% CI 3.30-22.33) in PTC patients.

Table 2 : Distribution of the study population according to presence or absence of excess iodine intake (n=111)

Iodine intake represented by urinary iodine concentration in microgram/liter (µg/l)	PTC patients (n=53)		Healthy Volunteers (n=58)		OR (95% CI)	*p*-value
	n	%	n	%		
Excess iodine intake (Urinary iodine level ≥200 µg/l)	42	79.3	18	31.0	8.48 (3.30-22.33)	0.001[s]
Normal or low iodine intake (Urinary iodine level <200 µg/l)	11	20.7	40	69.0		

s = significant

p-value reached from Chi-square test

DISCUSSION

Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid carcinoma, and the most common established risk factors for PTC are head-neck irradiation, a positive family history, and a few genetic disorders. In recent years, the global incidence of PTC has increased, and lifestyle changes that have occurred include the avoidance of head neck irradiation and global iodine fortification of salt and food to avoid thyroid disorders. According to information from the archives of the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), the number of new PTC patients is also increasing in the Bangladeshi population. The number of new patients with differentiated thyroid carcinoma (DTC) in the last decade (2010–2019) was 4666, which was 14.8 times higher than the decade 1990–1999. The Bangladesh government introduced iodine-fortified dietary salt throughout the country in 1995. Evaluation is needed to ascertain whether the proportion of iodine in iodized salt is within the healthy limit or is excessive enough to cause over-iodization. Evaluation is also necessary to determine the possibility of any association between excess dietary iodine intake and the occurrence of PTC.

Lee et al. (15) showed that the mean age was 44.7±12.3 years in PTC, which is comparable with the current study. Another study by Choi et al. (16) found the mean age was 48.9 years in patients with thyroid cancer and 48.0 years in those without thyroid disease, which is higher than the present study. Here it was observed that the age of the majority of PTC patients was in the third and fourth decades of life. A study by Kim et al. (16) observed that the mean age was 47.7±12.4 years in the PTC group and 47.8±11.3 years in the healthy group. The distribution of two matching variables, age and gender, was not significantly different between the PTC and healthy groups, which is also higher than the present study. The higher mean age and age range obtained by the studies of the above authors may be due to geographical variations, racial, ethnic differences, and genetic causes, which may significantly influence their study subjects.

It was discovered that women dominated PTC in the current study. However, the difference was not statistically significant (p > 0.05) between the two

groups. The study by Choi et al. (16) showed the proportions of female subjects were 86.4% in the PTC group and 51.8% in subjects without thyroid disease. Similar observations were also noted regarding the PTC predominance in female subjects (17, 18, 19).

Regarding body weight, a study by Lee et al. (19) suggested that the prevalence of PTC is supposed to be related to obesity, which may affect the prognosis for PTC patients. Middle-aged, morbidly obese people are more vulnerable to PTC. However, the mechanisms implicated in the association between obesity and PTC are a matter of debate. They found a positive association between body mass index and the BRAF mutation and supported the hypothesis that excessive body weight influences tumor progression. Another study by Hwang et al. (20) suggested that body weight gain, as well as an annual elevation in the obesity indicators in middle-aged adults, have significant effects on the occurrence of PTC. Their results indicated that the PTC risk increases with rapidly increased weight and body mass index in comparison to stable body weight during the transition from middle-aged to late adulthood. Moreover, the effects of increases in weight or obesity on the risk of developing PTC with a tumor size of one centimeter are evident, suggesting that environmental or nutritional factors, rather than improved screening strategies for small tumors, should be a focus. Postmenopausal women show increased PTC risks attributable to middle-aged weight gain, supporting the need for intensive weight management. By considering modifiable aspects of weight change during adulthood, their results can provide substantial evidence for prioritizing the primary prevention of PTC about weight gain and mid-life obesity.

Most iodine absorbed in the body eventually appears in the urine. Therefore, urinary iodine concentration is a good marker of recent dietary iodine intake. In individuals, urinary iodine levels can vary somewhat from day to day and even within a given day; however, various studies have convincingly demonstrated that a profile of iodine concentrations in the morning or other casual urine specimens (child or adult) provides a sufficient assessment of a population's iodine nutrition status. Round-the-clock urine samples are difficult to collect and are usually not necessary. Moreover, urinary iodine/creatinine ratios are unreliable, particularly when protein intake and consequently creatinine excretion is low (21).

In the current study, it was observed that the mean urinary iodine concentration was significantly ($p < 0.05$) higher in the PTC group than in the healthy group. A case-control study in China reported the median urinary iodine concentration was 517.2 microgram/Liter in PTC patients compared to 194.3 microgram/Liter in a control group (22). Another study in Korea reported a mean urinary iodine level of 786.0 microgram/Liter in PTC patients compared to 112.0 microgram/Liter in the control group (15). The urinary iodine concentration in a spot urine sample is regarded as a sensitive biomarker of excessive iodine intake, but the urinary iodine concentration alone does not adequately clarify the role of iodine intake in thyroid cancer or disorders (23).

It was observed that a remarkable number of participants in both the PTC group (42 out of 53) and healthy comparison group (18 out of 58) had biochemical evidence of excess iodine intake as their urinary iodine concentrations were 200 microgram/liter or above. Excess iodine intake significantly ($p < 0.05$) increased with 8.48-fold odds (95% CI 3.30-22.33) in PTC patients. The findings of this study raise the suspicion that excess iodine intake may have a causal relationship with the occurrence of PTC. The study by Choi et al. (16) elucidates the role of dietary iodine in the development of thyroid cancer or thyroid disorders and signifies the importance of estimating people's dietary iodine intake. Katagiri et al. (24) estimated the usual iodine intake in Japanese adults. They reported that the median iodine intake of each subject was 1,031 microgram/day, whereas the median iodine intake overall for all subjects in the survey was only 273 microgram/day in men. This was because the subjects consumed iodine-rich foods (kelp or soup stock) on at least one or more days of the 16 days. Yan et al.'s (25) study mentioned that high iodine intake is not a risk factor for PTC and that high urinary iodine is just a specific characteristic of this disease. Iodine retention was found in urinary iodine even with a large single dose iodine administration, e.g., oral administration or

injection of iodinated contrast (about 30 grams of iodine), and the urinary iodine levels were transiently increased after receiving iodinated contrast and soon reverted back to baseline either in euthyroid subjects or in PTC patients regardless of thyroidectomy operation (26, 27). In animal studies, long-term excess iodine intake could not induce the onset of PTC. Although epidemiological evidence suggests that excessive iodine intake is related to the occurrence of PTC, the role of iodine in this process has not been firmly established. Therefore, the authors of a few studies supported the conclusion that high iodine intake is not a risk factor for PTC, either with a large single dose of iodine administration or long-term high iodine intake (28, 29).

On the other hand, a good number of studies suggest the possibility of an association between excess iodine intake and the occurrence of PTC. It has been well known that the relationship between the iodine intake level of a population and the occurrence of benign thyroid diseases is U-shaped, with an increase in risk from both low and high iodine intake levels. Several types of benign thyroid nodules, e.g., nodular goiter (NG), are associated with either high iodine intake or chronic iodine deficiency (18, 30). Deficient iodine intake leads to endemic goiter, whereas excessive iodine intake results in iodine-induced hyperthyroidism and autoimmune thyroid diseases (31). The study by Guan et al. (32) suspected the association between urinary iodine levels and the risk of PTC occurrence but could not definitively be established in that research work. The case-control study done by Lee et al. (15) indicated that iodine nutrition status differs significantly between PTC patients and healthy controls, suggesting that iodine may be involved in the occurrence of PTC. Zhou et al. (18) suggested that higher urinary bisphenol A concentrations and excessive iodine intake are associated with NG and PTC. A study by Wang et al. (33) showed excessive urinary iodine concentrations in 67.0% of PTC patients compared to 19.9% in the healthy subjects. It demonstrated a significant association of high urinary iodine with benign thyroid nodules and PTC. The study by Huang et al. (34) showed excess urinary iodine concentrations in 44.3% of PTC patients compared to 22.2% of persons without PTC. Results of a few more studies demonstrated that urinary iodine levels in PTC patients were higher than those of healthy individuals (18, 25, 30).

Although the findings of a few previous studies are not conclusive or supportive of establishing any relationship between excess iodine intake and PTC, the findings of the current study suggest an increased risk of PTC in people with excess dietary iodine intake, which is also supported by a few other previous research studies.

CONCLUSION

This study revealed that a remarkable number of participants in both the PTC and healthy groups had biochemical evidence of excess dietary iodine intake as their urinary iodine concentrations were high. Moreover, a significant number of participants had biochemical evidence of excess iodine intake in the PTC group compared to that of the healthy group, which indicates a causal relationship between excess dietary iodine intake and the increased incidence of PTC. A large-scale study is needed to assess the iodine nutrition status of the Bangladeshi population and to ascertain the association between excess dietary iodine intake and PTC. Further studies are needed to assure whether the currently recommended iodine concentration in commercially available iodized dietary salt is within the healthy limit or is excessive enough to cause over-iodization.

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