Short Communications

Editorial Process: Submission:11/03/2023 Acceptance:06/06/2024

Analysis of Urinary Iodine Concentration in Differentiated Thyroid Cancer and Breast Cancer Cases

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Abstract

Iodine intake can affect thyroid and breast cells, and urinary iodine concentration (UIC) is an effective biomarker for iodine intake. **Objectives:** This study aimed to analyze the correlation between urinary iodine concentration in differentiated thyroid cancer (DTC) and breast cancer (BC) subjects. **Methods:** The study consisted of 80 subjects divided into case (20 DTC and 20 BC subjects) and control (40 subjects). Morning urine or spot urine was used for UIC measurement. **Results:** In thyroid cancer, UIC median patients and controls were 195.45 ± 133.61 µg/L and 145 ± 39.64 µg/L, respectively, with p =0.33. The UIC median of PTC subjects was significantly higher compared to FTC subjects, 227.12±130.98 µg/L versus 68.75±22.95 µg/L, p=0.00, and papillary thyroid cancer is closely related to a high iodine excretion in urine with contingency coefficient (c)=0.722. In BC patients, regardless of subtypes, breast cancer subjects showed a significantly lower iodine excretion level. The median of UIC patients and controls were 80.05 ± 38.24 µg/L and 144.25 ± 36.79 µg/L, respectively, p=0.000. **Conclusions:** Iodine urine concentrations strongly correlate with the type of DTC histopathology, and in BC subjects, IUC was significantly lower compared to the control.

Keywords: BRAF mutation- estrogen- excessive iodine intakes- iodine deficiency- histopathology

Asian Pac J Cancer Prev, **25 (6)**, 1869-1873

Introduction

Molecular iodine (I^2) plays an essential role in the physiology and pathology of many organs, including the mammary gland, stomach, prostate, and thyroid (Aceves et al., 2009). It is crucial for synthesizing thyroid hormones and maintaining the epithelial integrity of thyroid follicles. The thyroid gland preferentially internalizes iodide ions (I-). The mammary gland also takes up both I^2 and I- equally during pregnancy and lactation [1-4]. The sodium/iodide symporter (NIS), an integral plasma membrane glycoprotein that mediates iodide uptake, is expressed at its high level in the thyroid and lactating breast. However, studies in breast cancer cells reported that I^2 transport is a saturable process and NIS-independent [4-5].

Epidemiological studies reported that iodine deficiency, including high iodine intake, is a potentially relevant risk factor for thyroid cancer (TC) [6-9]. Thyroid cancer is more frequent in areas with iodine deficiency than possibly iodine excess [6,9]. Chronic iodine deficiency can be a risk factor for follicular and anaplastic thyroid cancer. Iodine deficiency is the leading risk factor for goiter and thyroid nodules [8].

Iodine supplementation suppresses the invasive potential of triple-negative basal breast cancer in vitro and animal experimental models [10]. It has also been hypothesized that iodine deficiency is causative in the developing BC [4,11-12]. Women with high iodine intake from seaweed have around a five times lower incidence of BC than the general population [12]. It has even been suggested that lower dietary iodine intake might be the reason for the increased incidence of BC, especially in young women in the United States [13-14]. The mechanism of action of iodine's anticancer effect related to breast cancer is proposed as an antioxidant, promoting differentiation and apoptosis [12]. A report from a clinical study of breast cancer patients found that iodine levels were significantly lower in women with diagnosed breast cancer than in normal breast tissue or benign fibroadenoma [14]. Iodine deficiency has been shown to alter the structure and function of rat mammary glands. The condition stimulates gonadotropin secretion, leading to a hyperestrogenic state (low estriol to estrone and estradiol ratio). This alteration may increase the risk of BC [11].

On the other hand, excessive iodine intakes increase

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thyroid cancer significantly in patients with papillary thyroid cancers [6,15]. A study reported in China, where the areas with excessive iodine intakes (median UIC >900 µg/L due to drinking water containing >100 µg/L iodine) than iodine-sufficient areas (69% vs. 53%), and it is associated with a high prevalence of BRAFT1799A mutation [6]. A Korean study reported PTC patients with excessive iodine intake (UIC≥500 µg/L) had an odd ratio (OR 6.240, 95% CI 2.080–18.726, p=0.001) which was a significantly more significant risk of having BRAF mutations than those with relatively low iodine intake (UIC<300 µg/L) had odd ratio (OR 4.761, 95% CI 1.764–12.850, p=0.002) [15].

Iodine is excreted in the urine. The concentration of iodine urine (UIC) is a biomarker of current iodine intake that can reflect recent changes in iodine status. World Health Organization (WHO) recommends using spot urine collections to measure UIC. It is an excellent biomarker of recent exposure to iodine in populations because it reflects intake from all dietary sources. The UIC measure of iodine nutrition is well-accepted, cost-efficient, and easily obtainable [8]. The study aims to analyze the correlation between UIC with DTC and BC incidence and the correlation with histopathology.

Materials and Methods

Study design

The study was a case-control; all participants obtained written informed consent. The ethics committee approved # 265/KEPK/2018, and all subjects obtained written informed consent to the work. The subjects consisted of twenty patients of DTC and twenty patients of BC. Blood and urine samples were taken for research purposes only. Subjects with normal urea, creatinine, and TSH levels were included. The controls were healthy ones. Histopathology data was taken from medical records. Thyroid cancer patients received L-thyroxin 100 µgr as suppressive therapy, and BC patients did not receive therapy yet.

Blood samples

Blood samples were used for urea, creatinine, and TSH measurements. The Enzymatic-UV Kinetic method to analyze urea levels and creatinine levels by colorimetric using the Jaffe-Kinetic method with a normal value of 10-50 mg/dl and 0.6-1.2 mg/dl for urea and creatinine, respectively. TSH measurement using a Chemiluminescence Immunoassay (CLIA) with a normal value of 0,27 – 4,20 µIU/mL.

Urine Iodine Concentration

Urine iodine concentration was taken from urine morning spot, and it's determined by the ammonium persulfate digestion method. The experiments were done twice. Ammonium persulfate (1000 µl) was added to 250 µl of the urine sample and heated in a dry bath at 90ºC for 60 minutes. Then cool to room temperature; add 2.5 ml of arsenic solution, mix, and incubate for 20 minutes. Ceric solution (300 µl) was added, mixed, and incubated for 30 minutes. Then, samples were read with a spectrophotometer with a wavelength of 420 nm (Sandell-Kolthoff reaction). The absorbance value and the calibration curve were obtained. The results were expressed as the median in µg/L. The result criteria are as follows: median of UIC > 200 µg/L as high, adequate 100-200 µg/L, and low <100 µg/L.

Statistical Analysis

Data are presented as mean ± standard deviation (SD); if data are not distributed normally, they are presented as median ± SD. The data was analyzed using the independent sample T-test, chi-square, and Crammer's V coefficient. Statistical significance is defined as $p< 0.05$.

Results

The characteristics of the subjects are shown in Table 1. All subjects had normal thyroid and kidney functions. The histopathological types of TC were 80% papillary (PTC) and 20% follicular (FTC). Breast cancer histopathological consisting of invasive breast carcinoma of no special type (IBC-NST) 65%, invasive lobular carcinoma (ILC)

Table 1. Characteristics of Thyroid and Breast Cancers Patients based on Thyroid and Renal Function, and Median of Urine Iodine Concentration

Characteristics	Thyroid Cancer		Control		Breast Cancer		Control	
	n	%	n	%	n	%	n	%
Age								
< 45 years	18	25	11	55	7	35	10	50
> 45 years	4	75	9	45	13	65	10	50
Sex								
Male	5	25	4	20	NA	NA	NA	NA
Female	15	75	16	80	20	100	20	100
Age (Mean ± SD)	53.3±10.78		36.60 ±14.32		45.8±7.43		42.4 ±9.48	
Ureum (mg/dl)	21.65 ± 4.62		16.90 ± 5.12		15.08 ± 7.3		17.24 ± 5.91	
Creatinine (mg/dl)	0.81 ± 0.18		0.85 ± 0.20		0.66 ± 0.20		0.80 ± 0.18	
TSH (µIU/ml)	1.47 ± 0.55		1.25 ± 0.86		1.45 ± 0.55		1.49 ± 0.86	
UIC	195.45 ± 133.61 µg/L		145 ± 39.64 µg/L		83.70 ± 41.65 µg/L		144.25 ± 36.79 µg/L	

Noted: UIC, (urine iodine concentration)

30%, and classic mucinous carcinoma (CMC) (5%). The histopathology type based on the classification of median UIC is shown in Table 2.

The median UIC of the DTC subjects and control were 195.45 ± 133.61 µg/L and 145 ± 39.64 µg/L, respectively, with p=0.33. The median UIC in PTC is very significantly higher compared to that in FTC (227.12±130.98 µg/L versus 68.75±22.95 µg/L) with p=0.00. The contingency coefficient correlation value between UIC and histopathology type of DTC strongly correlated (c=0.722). The median UIC in BC subjects and control was 83.70 ± 41.65 µg/L and 144.25 ± 36.79 µg/L, respectively. There was a significant difference in median UIC value between BC subjects and control (p=0.00). The relationship between the UIC and histopathology of BC is p=0.824. The UIC median did not significantly differ between BC types.

Table 2. The Histopathology Type of Thyroid and Breast Cancers Based on Median of Urine Iodine Concentration.

Thyroid Cancer		Papillary		Follicular		Total		Breast Cancer		NST		Lobular		Ductal		Non Hodgkin		Classic		Total	
		n	%	n	%	n	%			n	%	n	%	n	%	n	%	n	%	n	%
UIC	>200	9	56.3	0	0	9	45		>200	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	100-200	7	43.7	0	0	7	35	UIC	100-200	3	27.3	2	40	1	50	0	0	0	0	6	30
	<100	0	0	4	100	4	20		<100	8	72.7	3	60	1	50	1	100	1	100	14	70
Total		16	100	4	100	20	100			11	100	5	100	2	100	1	100	1	100	20	100

Noted: UIC, (urine iodine concentration); IBC-NST, (invasive breast cancer-no special type)

Discussion

The relationship between iodine supply and thyroid cancer incidence is still debatable [9,16]. In our study, the median UIC in DTC patients was not different from the controls. However, UIC was correlated with the histopathological type of DTC. Another study reported that iodine intake levels do not substantially influence the total incidence of DTC [9]. However, iodine may alter the thyroid-pituitary hypothalamus axis, leading to an increase and prolonged stimulation of follicular epithelium [2,9,16]. Moreover, dietary iodine may relate to genetic alterations in thyroid tumorigenesis [6,9,17-19]. Iodine deficiency and excess seem to promote cell division with an increased thyroid cell proliferation rate, where dividing cells may accumulate more genetic alterations that lead to the vulnerability of thyrocytes to mutagens, such as radiation and oxidative stress [2].

Chronic iodine deficiency has been associated with the development of goiter (hypertrophy and hyperplasia of follicular cells of the thyroid), which is attributed to excessive secretion of TSH by the pituitary and has been associated with thyroid cancer risk [6,9,15]. Animal studies have shown that mice fed an iodine-restricted diet are more likely to develop thyroid cancer [2,8-9]. The proliferation rate of thyroid cells increased significantly by 5 to 30-fold in both the high- and low-iodine diets compared to normal [2]. A study reported that a chronic iodine deficiency developed follicular hypertrophy, follicular cell hyperplasia, and thyroid hypertrophy [9]. Moreover, iodine deficiency is more effective as a tumor promoter than a carcinogenic effect [2,8-9,16,20].

On the other hand, chronically high iodine intake contributes to the accuracy of BRAF gene mutation, which may be a risk factor for PTC development [15,19,21-22]. BRAF mutations are identified in 60% of classic PTC, 80% of tall-cell variant PTC, and only 10% of follicular variant PTC [6,17-18,21,23]. In animal studies, iodine supplementation 16 times the normal concentration led to hyperplasia of follicular cells, organ hypertrophy, and a massively increased proliferation rate [2,16]. Patients from several regions in China with different iodine contents in natural drinking water demonstrated a significant

association of BRAF mutation in PTC with high iodine intake [6,23].

Urine iodine concentration was correlated with the histopathological type of DTC. The median UIC in PTC patients is significantly higher than the FTC (227.12±130.98 µg/L versus 68.75±22.95 µg/L) with p=0.000. The result is in line with other studies that reported a correlation between iodine intake and histopathology of thyroid cancer [17,23-25]. Epidemiological studies have reported a relationship between iodine intake and the histopathology types of TC [8-9,25]. The incidence of TC increases with high iodine intake and low intake. Chronic iodine deficiency and living in an endemic goiter area are associated with an increased risk of follicular histological cancer, and chronically high iodine intake may increase the risk of the papillary histological type of thyroid cancer [6,8-9].

On the other hand, dietary iodine has been proposed to be protective against breast cancer [4,11-12]. This study shows that the UIC level in breast cancer subjects was significantly low compared to the control group; the median UIC in the BC case and control groups were 83.70 ± 41.65 µg/L and 144.25 ± 36.79 µg/L (p= 0.000) respectively. Iodine deficiency may stimulate the gonadotropin secretion and produce a hyper-estrogenic state, producing relatively high estrone and estradiol production and relatively low estriol to estrone and estradiol ratio. This alteration in the endocrine state may increase the risk of BC [11-12]. An animal study demonstrated that iodine deficiency causes hyperresponsiveness to estradiol, which increases alveolar cell proliferation, abnormal nuclei changes, and increased iodine uptake within vacuoles in estradiol-stimulated mammary glands [12].

In conclusion, iodine has a vital role in developing thyroid and breast cancer diseases. Papillary thyroid cancer is closely related to a high iodine excretion in urine. Regardless of subtypes, breast cancer subjects showed a significantly lower iodine excretion level. The amount of iodine should be considered in the normal range to avoid an expected effect on the cells. Understanding iodine metabolism at the cellular and sub-cellular levels has improved our knowledge of iodine's role. Further studies are needed to cover the role of iodine in thyroid and breast cancer diseases.

Author Contribution Statement

All authors have critically reviewed and approved the final draft. The corresponding author is responsible for completing this information at submission. Conceptualization: AE and YK. Data curation: YK, YE, NAP. Formal analysis: DK, AA, and MI. Funding acquisition: YK. Methodology: AE.and YK. Writing - original draft: YK. Writing - review & editing: AE. [1, 2] [3, 4] [5, 6] [7] [8, 9] [10] [11] [12] [13-15] [16] [17-19] [20-25]

Acknowledgements

Universitas Andalas for the research grant #108/BPPT/PNP/FK-UNAND-2018, and Mrs. Fay Farley for English manuscript preparation.

Ethical approval

The research was approved by the appropriate ethical committees of Dr.M.Djamil Hospital, Padang-Indonesia, on 26 November 2018, # 265/KEPK/2018. All subjects obtained written informed consent to the work.

Conflict of interest

All authors declare there is no potential conflict of interest in this research.

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