The Relationship Between Iodine Status and Thyroid Stimulating Hormone (TSH) and Free T4 (FT4) in Women of Childbearing Age in Wonogiri Regency

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Abstract. The urinary iodine concentration (UIC) is the most common indicator for assessing the population's iodine status. Urinary iodine does not provide information about thyroid function directly. However, iodine status is an important determinant of thyroid disorders in women of childbearing age. This study aimed to know the relationship between iodine status and thyroid function using indicators of stimulating thyroid hormone (TSH) and free T4 (FT4) levels in women of childbearing age in Wonogiri Regency. A community-based cross-sectional study was conducted in Kismantoro and Slogohimo sub-districts, Wonogiri Regency. A simple random sampling procedure was used to select the study participants. A total of 170 women aged 15–49 years were assessed for UIC, and serum TSH and FT4 levels. The ammonium persulfate digestion method measured urinary iodine concentration (UIC). Serum TSH and FT4 levels by enzyme-linked immunosorbent assay (ELISA). Variables with nominal scales were presented as frequencies and percentages. Correlation analysis was done to find an association between variables. A p-value < 0.05 was considered significant with a CI of 95%. The median UIC was 247.45 μg/L (232.5–1004), indicative of more than adequate. The mean TSH (2.04 ± 2.24 μIU/ml) and FT4 (1.31 ± 0.30 ng/dl) concentrations were within normal reference ranges. The UIC no significantly correlated with serum TSH $p = 0.664$ ($p > 0.05$), FT4 $p = 0.845$ ($p > 0.05$) levels and thyroid functions $p = 1.000$ ($p > 0.05$). Finally, iodine intakes assessed by UIC in our study of women of childbearing age were regarded as sufficient in Wonogiri Regency, and no correlation was found between UIC and thyroid function test.

Keywords: iodine · iodine status · urinary iodine concentration · TSH · FT4 · thyroid function

1 Introduction

Iodine is an essential micronutrient for appropriate thyroid chemical biosynthesis, thyroxine (T4) and triiodothyronine (T3). The thyroid hormone manages cellular oxidation, energy metabolism, and basal metabolic state, particularly neurological growth and development during pregnancy and early infancy [1].

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Iodine deficiency during pregnancy can cause serious health problems such as miscarriage, neurological impairment, congenital hypothyroidism, stillbirth, low birth weight, poor cognitive function, decreased intelligence, and delays in intellectual development in infants and children [2–4]. In addition to the consequences of iodine deficiency, the epidemiological and clinical data from different regions and countries show the relationship between high iodine intake and thyroid diseases [5, 6].

Consumption of salt circulating and marketed in Wonogiri Regency still did not meet requirements according to SNI (Indonesian National Standard) [7]. Wonogiri Regency 2016 was declared a moderate endemic area. Goitre and cretinism were spread over 25 sub-districts or 34 public health centres, and 55% of goitre sufferers came from Kismantoro and Slogohimo sub-districts [8]. However, factors related to UIC among women of childbearing age in the Wonogiri Regency have not been very much studied. Assessment of accurate iodine status in the population must inform clinical research and public health policy on the impacts of iodine nutrition [9].

Since most of the iodine absorbed through the walls of the digestive tract is excreted in the urine, urinary iodine directly reflects recent iodine intake and is the primary biomarker used indicator to assess population iodine status [8, 10]. Urinary iodine concentration (UIC) is less well studied to estimate iodine status in individuals. There is no clear agreement on determining an individual's iodine status by measuring urinary iodine [11]. This indicator does not give direct information about the functioning of the thyroid gland [12].

Iodine is an essential micronutrient required for thyroid hormone biosynthesis, [11] Thyroid stimulating hormone (TSH) acts as a major regulator by controlling the expression of thyroid-specific genes involved in thyroid hormone biosynthesis [13, 14]. Although such use is usually problematic, clinical laboratory tests of thyroid function (including serum levels of TSH and thyroid hormones) are sometimes used as indicators of iodine status, [9] it is also considered a potential biomarker for assessing iodine status [11].

This study aimed to know the relationship between iodine status and thyroid function using indicators of TSH and FT4 levels in women of childbearing age. The results can be useful for the IDD elimination program.

2 Materials and Methods

A cross-sectional study was conducted in Kismantoro and Slogohimo sub-districts, Wonogiri Regency, in March-December 2019 after getting approval from the Health Research Ethics Committee, National Institute of Health Research and Development (HREC-NIHRD) on March 14, 2019 (Nomor: LB.02.01/2/KE.074/2019).

The simple random sampling procedure was used to select the study participants who numbered 170 women of childbearing age between 15–49 years old, living in the study area (Kismantoro and Slogohimo sub-districts) without chronic disease based on the results of our physical examination. Written informed consent was obtained from all participants.

Iodine concentrations were measured in urine samples collected in spot urine specimens. The urinary iodine determination method uses ammonium persulfate digestion. Using the developed iodine standard curve, the UIC in the samples were

obtained, and WHO/ICCIDD/UNICEF reference medians for UIC were used to classify iodine intake as 'severe deficiency' (<20 μg/L), 'moderate deficiency' (20–49 μg/L), 'mild deficiency' (50–99 μg/L), 'adequate' (100–199 μg/L), 'more than adequate' (200–299 μg/L) or 'excess' (≥300 μg/L) [15, 16].

A total 3 mL of venous blood was taken to measure TSH and FT4 levels. Serum TSH and FT4 levels were measured by the enzyme-linked immunosorbent assay (ELISA) method. Serum TSH levels were classified as 'low' (<0.3 μIU/ml), 'normal' (0.3–4.0 μIU/ml), and 'high' (>4.0 μIU/ml). Serum FT4 levels were classified as 'low' (<0.8 ng/dl), 'normal' (0.8–2.0 ng/dl), and 'high' (>2.0 ng/dl). Participants were classified into five groups according to their thyroid function test results: 'overt hypothyroidism' (TSH > 4.0 μIU/ml and FT4 < 0.8 ng/dl), 'subclinical hypothyroidism' (TSH > 4.0 μIU/ml and FT4 0.8–2.0 ng/dl), 'euthyroidism' (TSH 0.3–4.0 μIU/ml and FT4 0.8–2.0 ng/dl), 'overt hyperthyroidism' (TSH < 0.3 μIU/ml and FT4 > 2.0 ng/dl), and 'subclinical hyperthyroidism' (TSH < 0.3 μIU/ml and FT4 0.8–2.0 ng/dl) [17].

Descriptive analysis was performed to describe the variable characteristics of subjects. Variables with nominal scales were presented as frequencies and percentages. Correlation analysis was done to find the association between variables. A p-value < 0.05 was considered significant with a CI of 95%.

3 Results

One hundred seventy women of childbearing age were involved as participants in this study. Most participants have completed nine years of education, and 45.3% finished junior high school. Only 26.5% of the participants were in employment, including laborer/farmworkers, farmers, private employees, and entrepreneurs, while 73.5% were unemployed. An estimated 31.2% of UIC in women of childbearing age was indicative of 'more than adequate' (individual UIC 200–299 μg/L), whereas 0.0% of participants was indicative of 'severe deficiency' iodine status (individual UIC < 20 μg/L) (Table 1).

Based on the results of measurements of both serum TSH and FT4 levels in this study, 83.3% dan 100% of participants were classified in 'normal' status (individual serum TSH and FT4 levels between 0.3–4.0 μIU/ml and 0.8–2.0 ng/dl, respectively) (Table 1).

The median UIC among women of childbearing age was 247.45 μg/L (232.5–1004), whereas the mean serum TSH and FT4 levels were 2.04 ± 2.24 μIU/ml and 1.31 ± 0.30 ng/dl, respectively (Table 2).

The Pearson correlation test was used to analyze associations between UIC and serum TSH levels and the Spearman correlation test was used to analyze associations between UIC and serum FT4 levels in women of childbearing age. The UIC no significantly correlated with serum TSH $p = 0.664$ ($p > 0.05$) and FT4 $p = 0.845$ ($p > 0.05$) levels (Table 3).

The UIC in women of childbearing age was indicative of 'adequate' (individual UIC 100–199 μg/L), 7.8% of participants were classified in subclinical hyperthyroidism, 80.3% euthyroidism, and 11.7% subclinical hyperthyroidism. The UIC was indicative of 'more than adequate' (individual UIC 200–299 μg/L), 7.5% of participants were

Table 1. Characteristics of Participants

Variable	Category	n	%
Education	No formal schooling	2	1.2
	Not completed elementary school	3	1.8
	Elementary school graduate	46	27.1
	Junior high school graduate	77	45.3
	High school graduate	37	21.8
	Diploma/Bachelor's degree	5	2.9
Employment	Unemployed	125	73.5
	Laborer/Farmworkers	23	13.5
	Farmers	4	2.4
	Government employees	0	0.0
	Private employees	10	5.9
	Entrepreneurs	8	4.7
	Pensioners	0	0.0
UIC	<20 μg/L	0	0.0
	20–49 μg/L	5	2.9
	50–99 μg/L	12	7.1
	100–199 μg/L	51	30.0
	200–299 μg/L	53	31.2
	≥300 μg/L	49	28.8
Serum TSH levels	Low	12	7.1
	Normal	145	85.3
	High	13	7.6
Serum FT4 levels	Low	0	0.0
	Normal	170	100
	High	0	0.0

UIC: urinary iodine concentration; TSH: thyroid stimulating hormone; FT4: free T4.

classified as subclinical hyperthyroidism, 88.6% euthyroidism, and 3.7% subclinical hyperthyroidism. The UIC was indicative of 'excess' (individual UIC ≥ 300 μg/L), 10.2% of participants were classified as subclinical hyperthyroidism, 81.6% as euthyroidism, and 8.1% as subclinical hyperthyroidism. The Kolmogorov-Smirnov test was performed to analyze 2 x (>2) contingency tables to calculate the extent of the relationship between UIC and thyroid function. The UIC no significantly correlated with thyroid function $p = 1.000$ ($p > 0.05$) (Table 4).

Table 2. Distribution of Urinary Iodine Concentration, Serum Thyroid Stimulating Hormone, and Free T4 Levels

Variable	*n*	*Mean*	*Std. Deviation*	*Min*	*Median*	*Max*
UIC (μg/L)	170	247.45	142.92	0.27	232.50	1004
TSH (μIU/ml)	170	2.04	2.24	0.01	1.77	25.33
FT4 (ng/dl)	170	1.31	0.30	0.80	1.31	1.98

UIC: urinary iodine concentration; TSH: thyroid stimulating hormone; FT4: free T4.

Table 3. Correlation of Urinary Iodine Concentration with Serum Thyroid Stimulating Hormone and Free T4 Levels

Variable	n	TSH		FT4	
		r	*Sig (2-tailed)*	r	*Sig (2-tailed)*
UIC	170	-0.034	0.664^{α}	0.015	0.845^{β}

$^{\alpha}$Pearson correlation significance $p < 0.05$; $^{\beta}$Spearman correlation significance $p < 0.05$; UIC: urinary iodine concentration; TSH: thyroid stimulating hormone; FT4: free T4.

Table 4. Association between Urinary Iodine Concentration with Thyroid Function

UIC Category	Thyroid Function						Total	
	Subclinical Hypothyroidism		Euthyroidism		Subclinical Hyperthyroidism			
	n	%	n	%	n	%	n	%
Moderate def[1]	0	0.0	5	100	0	0.0	5	100
Mild def[2]	0	0.0	12	100	0	0.0	12	100
Adequate [3]	4	7.8	41	80.3	6	11.7	51	100
More than adequate[4]	4	7.5	47	88.6	2	3.7	53	100
Excess [5]	5	10.2	40	81.6	4	8.1	49	100
Total	13	7.6	145	85.2	12	7.0	170	100

p (A Kolmogorov-Smirnov test was performed to analyze 2 × (>2) contingency tables) $^{(1+2),(3+4+5)} = 1.000$; UIC: urinary iodine concentration; def: deficiency.

4 Discussion

Most countries have implemented universal salt iodization (USI) programmes, and two-thirds of the world's population is protected by iodized salt. To assess iodine nutrition at the population level, there are two most commonly used approaches, estimation of

the household penetration of adequately iodized salt and measurement of urinary iodine concentrations [8, 15].

Because more than 90% of ingested iodine for individuals in positive iodine balance is ultimately excreted in the urine, urinary iodine is an excellent indicator of recent iodine intake. Collecting twenty-four (24) hour urine specimens in field research is impractical. Urinary iodine can be assessed in spot urine specimens from a representative sample of the target population [15, 18, 19]. The World Health Organization (WHO) recommends monitoring the iodine status using UIC of school-age children in the population [20, 21]. Many countries are beginning to perform studies on high-risk population groups, i.e., younger children, pregnant women, and women of reproductive age; however, data are narrow [22–25].

In school-age children and non-lactating or non-pregnant women, a median UIC range of 100–299 μg/L shows that iodine deficiency does not occur in a population with any more than 50% of urine samples below 100 μg/L and not more than 20% of samples should have an iodine concentration below 50 μg/L [26–28]. Kismantoro and Slogohimo sub-districts, Wonogiri Regency has no iodine deficiency, 10% of urine samples in women of childbearing ages below 100 μg/L and 2.9% of urine samples below 50 μg/L (Table 1). The WHO, UNICEF, and ICCIDD recommended median UIC for populations of 100–200 μg/L, and the range of 200–299 μg/L indicates 'more than adequate iodine intake [15]. The findings of this study, the median UIC in women of childbearing age, was indicative of 'more than adequate', whereas the mean of serum TSH and FT4 levels were in 'normal' status, respectively (Table 2). The 'more than adequate range of a median UIC has raised concerns about the potentially adverse effects of high iodine intake on normal thyroid function. However, a study assessing iodine status and thyroid function in 2013 found that the median UIC range of 100–299 μg/L was not associated with any thyroid dysfunction [28].

Iodine is an essential micronutrient required for thyroid hormone biosynthesis, [11] Thyroid stimulating hormone (TSH) acts as a major regulator by controlling the expression of thyroid-specific genes involved in thyroid hormone biosynthesis [13, 14]. In conditions of adequate dietary iodine intake, no more than 10% of iodine absorbed in the gut is retained by the thyroid gland, with the majority of remaining iodine (>90%) excreted in the urine. For this reason, urinary iodine measurements from spot urine samples collection is currently the internationally recognized method for assessing and monitoring population iodine status [3, 15, 29]. In our study, the UIC not significantly correlated with serum TSH ($p > 0.05$) and FT4 ($p > 0.05$) levels (Table 3). Thyroid stimulating hormone (TSH) is used as part of newborn screening programs to detect congenital hypothyroidism in infants in many developed countries [11]. For other population groups, mean TSH values do not adequately discriminate between iodine-deficient and iodine-sufficient populations [30]. A negative relationship has been shown between UIC and TSH levels measured in the neonatal umbilical cord blood ($r = -0.20$, $p = 0.02$) [31]. For the reasons described in this finding, neonates thyroid has a low iodine content, and hence neonatal iodine turnover rate in the thyroid is much higher than in adults and children. The neonatal TSH would be a sensitive indicator of population iodine deficiency. However, when this has been studied, it has been known that the increase in the serum level of TSH seen is not enough for this to be an adequate marker. Additionally,

the serum level of TSH in adults and children may increase slightly in iodine deficiency, but concentrations commonly remain within the reference interval, leading it to a fairly insensitive marker [11]. In infants, serum thyroid hormones (total T3 & T4; free T3 & T4) are elevated at twenty-four hours following birth in term infants in response to a physiologic spike in TSH that occurs immediately after birth. Therefore, age-normative values are required to interpret thyroid function in newborns [9].

Except in areas of severe iodine deficiency, thyroid hormone concentrations are not recommended to indicate iodine status. Changes in thyroid hormone levels are often within the normal reference ranges, and overlapping with iodine-sufficient populations is large enough to make thyroid hormone values an insensitive measure of iodine nutrition [30]. Thyroid hormones are inadequate biomarkers of iodine status in individuals and populations [11]. As a part of physiologic changes, the glomerular filtration rate increases during the first trimester of pregnancy; a study expecting different results tries to observe better iodine status during this trimester compared with the other two. In the current cohort study of pregnant women, the iodine intakes were sufficient, and no correlation was found between UIC and thyroid function tests [32].

The UIC no significantly correlated with thyroid function ($p > 0.05$) (Table 4). For the reasons described in this section. The thyroid gland secretes the thyroid hormones in response to TSH, a peptide hormone produced by the anterior pituitary. The majority of triiodothyronine (99.70%) and thyroxine (99.97%) are tightly bound to thyroxine-binding globulin (TBG) and other plasma proteins, and only a minute fraction of thyroid hormones is unbound or free T4. Free T3 is regarded as the biologically active thyroid hormone in circulation. Serum TSH levels are the most sensitive measurements for thyroid dysfunction [33]. Subclinical hypothyroidism is mildly elevated serum TSH, but FT4 levels are within the normal reference laboratory range. In overt hypothyroidism, there is no feedback inhibition of the intact pituitary, and serum TSH is always elevated, whereas serum FT4 levels are low [34]. Serum total and free T3 levels usually do not decrease until hypothyroidism is quite severe because elevated TSH stimulates the release of T3 from the thyroid gland [9]. As well as subclinical hyperthyroidism and overt hyperthyroidism, with the opposite mechanism. Severe nonthyroid disease can cause changes in serum thyroid hormone and TSH levels, even in individuals with normal underlying thyroid function. Serum TSH and T3 levels characteristically decline during the acute stage of illness, and T4 may also decrease as the illness progresses. During the recovery period, serum TSH levels may transiently rise above the reference range before thyroid function tests normalize [9].

Mechanisms of adaptation of the thyroid gland to iodine deficiency in several ways. Iodine deficiency can cause increased serum TSH levels, which will drive increased avidity of the thyroid gland for iodine, and T3 to T4 ratios increased [35]. Increased conversion of T4 into T3 in the peripheral and enlargement of the thyroid gland. In severe iodine deficiency, these mechanisms of compensatory response may prove inadequate and can develop hypothyroidism [9].

In areas of moderate-to-severe iodine deficiency, the serum level of TSH may be increased compared with in iodine-sufficient areas, the serum level of T3 may be slightly high and the serum level of T4 may be slightly low. There are many interindividual differences in the ability to adapt the thyroid gland in areas of severe iodine deficiency

[9] following the successful implementation of salt iodization programmes in areas of severe iodine deficiency [36]. Therefore, thyroid function tests (including serum thyroid hormone and TSH) are not considered sensitive indicators of iodine status in the population [9, 30].

In some areas of mild-to-moderate iodine deficiency, in older people, the serum level of TSH may be lower than in areas of iodine-sufficient due to the increased prevalence of hyperthyroidism from autonomously functioning thyroid nodule (AFTN) in areas with insufficient iodine intakes [9, 37]. Chronic exposure to excess iodine can cause thyroid dysfunction in some vulnerable individuals; the serum level of TSH may be slightly increased in areas with excessive iodine intake [9].

Urinary iodine concentration in the individual can vary day-to-day or even within the same day [38]. These variations tend to even out within populations and provide a useful measure of the iodine status of populations but cannot be reliably measured at individual levels [39]. The UIC does not indicate direct information about thyroid function [12].

5 Conclusion

Iodine intakes assessed by UIC in our study of women of childbearing age were regarded as sufficient in Wonogiri Regency, and no correlation was found between UIC and thyroid function test. The UIC no significantly correlated with thyroid function ($p > 0.05$).

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