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Iodine, Cyanide, Thyroid Stimulating Hormone and Free Thyroxine Levels

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A B S T R A C T

Nutrients that play an important role in the formation of thyroxin (T4, pro-hormone) and triiodotironim (T3, the active hormone) which are elements of the formation of thyroid hormone in thyroid follicle cells are iodine. However, iodine absorption is affected by goitrogen, one of which is cyanide. This study is an observational analytical study with a Cross Sectional design on 50 hyperthyroid patients undergoing treatment at the Magelang Health Research and Development Center. Intake data was obtained by the 2x24-hour recall method while TSH and FT4 data were obtained from laboratory examinations conducted at the Magelang Health Research Institute. The results showed that there was a relationship between iodine intake and TSH levels of hyperthyroid patients ($p<0.05$). Meanwhile, iodine intake with FT4 levels was not significant ($p=0.319$). There is a meaningful relationship between iodine intake and TSH levels of hyperthyroid patients.

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INTRODUCTION

Hyperthyroidism is a clinical syndrome due to an increase in free serum Thyroxine (FT4) and/or free triiodothyronine (FT3) as a result of hypermetabolic conditions (LiVolsi & Baloch, 2018). Excessive T4 and T3 will cause suppression of Thyroid Stimulating Hormone (TSH) levels (Pandiyan et al., 2018). TSH levels will decrease with age, while free T4 levels will decrease (Park et al,., 2018). The serum TSH level of hyperthyroid patients is <0.4 μIU/mL (Courtesy & Nurcahyani, 2015). The prevalence of hyperthyroidism in iodine-deficient populations ranges from 0.7 – 1.8% and in people with mild iodine deficiency by 2-15% (Biondi & Cooper, 2018) Based on health research data in 2013, the prevalence of hyperthyroidism in Indonesia is 0.4% and for the Central Java region is 5% (Ministry of Health, 2013). In general, iodine is associated with the occurrence of hyperthyroidism (Taylor et al., 2018). The incidence of hyperthyroidism is more common in women than in men, where the incidence ratio is 5:1 (Uygur et al., 2018).

Iodine is an integral component of thyroid hormone (Waught et al., 2019; Sun 2017). This is based on the fact that iodine is a component of Thyroxin and triiodothyrim which play an important role in the synthesis of thyroid hormone in thyroid follicle cells (Rayman, 2018). Iodine consists of 65% by weight of thyroxin and 59% of and triiodotironin with a half-life of thyroxin of about 5 days and for triiodothine about 1.5-3 days (Zimmermann et. al., 2008)

Iodine deficiency is one of the common nutritional problems that affects about 35% - 40% of the world's population and is a health problem in 50 countries (Maniakas et al., 2018). This is influenced by the uneven distribution of iodine globally and more than one billion people around the world are domiciled and live in iodine-deficient areas with the most vulnerable populations being those who live in mountainous areas such as Southeast Asia, South America and Central Africa (Taylor et al., 2018). The concentration of iodine in plants is influenced by the iodine content of the soil. So that plants that grow in soil that is sufficient iodine will have an iodine content of about 1 mg/kg while plants that grow in areas that are low in ioium will have a lower iodine content of about 10% μg/dry weight (Zimmermann et al., 2008). Areas that experience frequent flooding are at risk of having lower soil iodine content (Zimmermann et al., 2008). This event is attributed to iodine erosion from the soil due to vegetation loss, overgrazing and deforestation (Sun et al., 2017).

Iodine metabolism in the human body goes through several circuits involving the hypothalamus, pituitary, thyroid gland and blood (Zimmermann et al., 2008). The absorption of iodine in healthy individuals is fast and easily absorbed in the form of iodide in the digestive tract (stomach and duodenum) of about >90%, while iodine is in the intestine and is almost completely absorbed in the intestine (Duntas, 2018). Iodine absorption is affected by the consumption of goitrogen. Goitrogenic substances are iodine antagonists that act on the thyroid gland (Reijden et al., 2017). Goitrogens will directly inhibit or block the uptake of iodine into the thyroid (Panth et al., 2018). Goitrogenic substances will directly affect the thyroid gland in the synthesis of thyroid hormones (Dewi, 2015). Foods that are classified as goitrogens include cabbage, kale, cassava, millet and taro

(Taylor, 2018). Cyanide acid contained in highly toxic foodstuffs, the body will convert it into isothiocyanate (SCN-) which is excreted through urine and if buried in the thyroid gland will interfere with the synthesis of thyroid hormones (Dewi, 2015). The safe cyanide content is 10 mg/kg (ppm) dry weight (Ningtyias et al., 2015). Goitrogenic substances will directly and indirectly affect the functional work of the thyroid gland (Zimmermann et al., 2008).

The relationship between iodine intake and thyroid disorders in U-shaped populations due to insufficient or excessive iodine intake can impair thyroid function. A small increase in intake in populations that were previously iodine deficient can change the pattern of thyroid disease (Zimmermann & Boelaert, 2015). Iodine deficiency and excess will cause thyroid disorders, including hyperthyroidism (Taylor et al. 2018). Excessive iodine consumption will trigger the wolf-chaikoff effect, which for 24 hours after consumption will lead to a reduction in the synthesis of thyroid hormones (Knezevic et al., 2020). Low concentrations of thyroid hormones will trigger negative feedback resulting in the release of thyroid releasing hormone (TRH) and TSH from the pituitary gland (Cicatieello 2018). But on the other hand, when the thyroid hormone contained in the blood increases, it will result in an emphasis on TSH (Kumorowulan et al., 2019). The initial screening to establish the diagnosis of hyperthyroid incidence and hyperthyroid severity is an examination of serum TSH levels (Uygur et al., 2018). Therefore, this study aims to analyze the relationship between iodine intake and TSH and FT4 levels in hyperirioid patients.

METHODOLOGY

This research has met the ethical criteria and has been approved by the ethics committee of Sebelas Maret University No. 013/UNS27.06/KEPK/EC/2020. Samples involved in previous studies have signed informed consent. This research is an observational research with a cross sectional design approach which was carried out in February – July 2020 at the Magelang Health Research and Development Center. The research sample of 50 people was calculated based on the finite population equation (Rodriguez del Aquila, 2013) and selected based on predetermined inclusion and exclusion criteria. The inclusion criteria consisted of adult hyperthyroid patients, both female and male, with an age range of 18-59 years who underwent treatment at the Magelang Health Research and Development Center, had serum THS levels of < 0.3 µIU/mL with stroma or not, and received treatment or not.

Iodine intake was obtained through a 2 x 24-hour recall interview process on the day of the stabbing, then analyzed using the nutrisurvey application and the composition table of food ingredients, while the cyanide intake was obtained through SQ-FFQ which was then compared with the cyanide content of food ingredients in the previous study. Blood collection of 3 cc by experts for the purpose of TSH and FT4 examination at the laboratory of the Magelang Health Research and Development Center using the ELISA method. The data obtained was analyzed using the SPSS application version 25. The normality test is similar to the Shapiro-wilk test, the data is stated to be distributed nrmal if $p>0.05$. Numerical data is presented in the form of mean±SD while for categorical data it is presented in the form of frequency and percentage. The relationship between iodine intake and TSH and FT4 levels was analyzed using the Spearman Rank test.

RESEARCH RESULTS

The characteristics of the subjects in this study included age, gender, nutritional status, education, average iodine intake, cyanide intake and average TSH and FT4 levels. Distribution of characteristics of 50 respondents in this study are presented Table 1.

Table 1. Distribution of Characteristics of Respondents

Variabel	mean±SD	Frequency (%)
Age	40,36±10,20	
Gender		
Man		8 16,0)
Woman		42 (84,0)
Nutritional Status	23,09±3,71	
(BMI)		3 (6,0)
That		25 (50,0)
Normal		6 (12,0)
Overweight		15 (30,0)
Obesity I		1 (2,0)
Obesitas II		
Education		
Finishing Elementary		14 (28,0)
School		2 (4,0)
Not Finishing		9 (18,0)
Elementary School		16 (32)
Junior High School		9 (18,0)
Graduation		
Tamat SMA		
Bachelor		
Average Iodine Intake	595,73±461,91	
Kuranag (<80%)		3 (6%)
Adequate (80-110%)		6 (12%)
Over (>110%)		41 (82%)
Average Cyanide Intake	0,300±1,550	
Track-Track TSH	0,22±0,47	
Low (<0.3 mIU/mL)		40 (80,0)
Nrmal (0.3-4.0 mIU/mL)		10 (20,0)
FT4 Average	2,50±2,05	
Low (0.8 ng/dL)		4 (8,0)
Normal (0,8-2,0 ng/dL)		24 (48,0)
Over (>2.0 ng/dL)		22 (44,0)

Table 2. Relationship between iodine and cyanide intake with TSH and FT4

Independent Variabel	Dependent Variabel			
	TSH		FT4	
	r	p	r	p
Recall iodium	-0.287	0.044	0.164	0.256
Sianida	0.077	0.597	-0.112	0.439

DISCUSSION

Table 1 shows the mean values of TSH and FT4 in this study of 0.22 µIU/ml and 2.50 ng/dL, respectively. TSH levels are strongly influenced by the nutritional status of iodine either in excess or in deficiency (Yang et al., 2014). Excess or insufficient iodine intake has the same impact on thyroid function, because of the relationship between iodine intake and thyroid disorders in U-shaped populations (Zimmermann and Boelaert, 2015). The thyroid gland requires iodine intake >50 µg/day to maintain the state of euthyroidism. However, if the daily intake is below 50 µg/day, it will cause iodine reserves in the thyroid to be depleted (Niwattisawoq et al., 2017). The minimum recommended dose of iodine for thyroid hormone synthesis is 150 µg (Antonelli et al., 2020). Judging from the characteristic data in Table 1. 42% of the subjects of this study were female, where the average age of the study subjects was 40.36±10.20 years. The incidence of hyperthyroidism increases with age and more in women (De-Leo, 2016). The ratio of hyperthyroid incidence in women and men is 5:1.

Based on the data in table 1. 32% of respondents have a high school education background and 18% have a bachelor's degree. Based on research conducted by Sihombing et al (2021), it was concluded that individuals who have a higher education background (college) have a higher proportion of hyperthyroid incidence compared to respondents who have a high school education level. This could be due to the stress level factor. Oxidative stress is believed to have an important role in the occurrence of hyperthyroidism. Typical hypermetabolic conditions will cause the release of large amounts of reactive oxygen species (ROS) in peripheral tissues which in turn cause the release of ROS in the thyroid gland (Marino et al., 2018) and hydrogen peroxide (H2O2) produced by thyroid follicles during the biosynthesis of thyroid hormones (Pakdel et al., 2019). The release of this ROS will cause a breakdown of thyroid epitol cells that will result in exposure to autoantigens to the immune system that is dependent on tissue damage, which contributes to the clinical manifestations of hyperthyroid (Marino et al., 2018)

The bivariate analysis conducted showed that there was a relationship between iodine intake and TSH levels of hyperthyroid patients (r = -0.289, p = 0.042) (Table 2). In addition, this study shows that the relationship between iodine intake and TSH levels is in the opposite direction, which means that the high iodine intake of the sample, the lower the TSH level and vice versa. The average iodine intake of subjects was 595.73±461.91 µg, which when compared to the iodine needs of 15-59 years old, was only 150 µg/day (Rayman, 2018; Zimmermann et al., 2008). Excess iodine intake will trigger the Wolff-Chaikoff effect, for 24 hours after excessive iodine consumption there will be a temporary reduction in thyroid hormone synthesis. (Knezevic et al, 2020). Excessive iodine intake will develop into hyperthyroidism (Singh & Hershman, 2017). Individuals with diffuse nodular goiter and Grave's latent disease when excess iodine will cause hyperthyroidism (Knezevic et al 2020).

The results of this study are supported by research conducted by Zhao et al., (2014) which concluded that excessive iodine consumption will cause thyroid disease, one of which is hyperthyroidism through a long-term mechanism. A croos-sectional study conducted on adults in China living in areas with different iodine content concluded that urinary iodine concentration was positively associated with TSH values ($r=0.414$, $p=0.000$) and based on linear regression analysis of excess or underiodine intake had a significant relationship with TSH levels (Yang et al., 2014).

Studies in mice show that excess iodine intake will worsen thyroiditis which is estimated through 3 mechanisms, namely first, an increase in the immunogenicity of thyroglobulin molecules as a result of excess iodine intake. Second, excessive iodine intake induces reactive oxygen sspecies (ROS) which leads to increased expression of ICAM-1 which plays a role in the early stages of the inflammatory response in thyroid follicle cells. Finally, excessive iodine intake will lead to high H2O2 levels which will damage tyrocytes (Zhao et al., 2014).

Iodine is one of the micronutrients that are needed in life (Waught et al., 2018; Taylor et al., 2018). However, the distribution of iodine around the world is uneven, so more than one billion people live in areas that are classified as iodine deficient (Taylor et al., 2018). Food sources provide about 3-80 mg/serving of iodine, but this is also influenced by geochemical, soil, and cultural conditions. (Waugh et al., 2019). Iodine status is greatly influenced by the iodine content in food and the absorption of iodine in the body. One of the factors that affect iodine absorption is goitrogen. Goitrogen is an iodine antagonist that acts on the thyroid gland in several ways including inhibiting Sodium Iodide Symporter (NIS) on the baselateral membrane of the thyrocyte, disrupting the oxidation of iodide into iodine (I2) elements, disrupting iodine coupling in thyroglobulin and/or interfering with the production of T3 and T4 and their release into circulation (Reijden et al., 2017).

The bivariate analysis conducted showed that the cyanide intake with TSH and FT4 levels of hyperthyroid patients was statistically insignificant ($p>0.05$). Cyanide (HCN) is a toxic substance contained in several food ingredients which if consumed will be converted into isothiocyanate (SCN-) which is one of the substances classified as goitrogens (Dewi, 2015). Cyanide is a precursor of thiocyanate which is goitrogenic and is one of the risk factors for iodine deficiency disorders (GAKY) (Ningtyias et al., 2015). Research conducted by Wardani et al., (2018) concluded that goitrogenic consumption was statistically insignificant with the incidence of GAKY ($p=0.105$).

The ocean is the world's main iodine storehouse and the iodine content in the soil is much less than in the ocean. Seawater contains 50 μg of iodine/L (Waugh, 2019). Iodine levels in foodstuffs vary according to place, the sources of iodine that are often consumed by humans on average come from marine fish (80%), food/vegetable crops (80%), drinking water (19%), and non-marine animals (10%). Iodine levels in marine fish are higher due to the presence of good salinity conditions (salt content) for the growth of marine fish, which is around 3..5% (Muawanah, 2018). Beaches rich in seaweed have a higher iodine content (Waught, 2019). The iodine cycle in most areas is slow and incomplete, resulting in soil and groundwater experiencing iodine deficiency. The soil that lacks iodine will be overgrown with plants (grass) that will be consumed by livestock and then these livestock will be consumed by humans and will eventually experience iodine deficiency (Zimmermann et al., 2008). Food processing also affects iodine levels in foodstuffs. The cooking process such as boiling, baking will reduce iodine levels by about ≤10% (Zimmermann et al., 2008). The results of a study conducted by Rana & Raghuvanshi, (2013), cooking with boiling, baking, frying and cooking methods using microwave affected the loss of iodine levels by around 40.23%, 10.57%, 10.40% and 27.13%, respectively. The process of processing fish by frying will reduce the iodine content of fish by 25% and when burned will be reduced by 25%, boiled without being covered will be reduced by 56% (Muawanah, 2018). In addition, food processing can also affect the content of goitrogen (cyanide) in foodstuffs (Ningtyias et al., 2015).

CONCLUSIONS AND RECOMMENDATIONS

Excessive iodine intake significantly affects the TSH levels of hyperthyroid patients in GAKI endemic areas. Excessive iodine intake over a long period of time will affect the production of thyroid hormones. Thus, insufficient or excessive iodine intake will have an impact on the production of thyroid hormones.

The intake of goitrogen, especially for cyanide, was statistically insignificant with TSH or FT4 levels in hyperthyroid patients. In addition, the food processing process will affect the iodine content contained in food. Further research is needed regarding the content of goitrogens in food consumed by hyperthyroid patients and the iodine content of food based on the way of processing of foodstuffs.

ADVANCED RESEARCH

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