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Thyroid Dysfunction, Total Cholesterol Levels and Anthropometric Status in Women of Reproductive Age in Iodine Deficient Area of Prambanan Sub-District, Sleman Regency, Indonesia

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ABSTRACT

This study aimed to determine the relationship between thyroid dysfunction with Total Cholesterol levels (TC), Body Mass Index (BMI), Waist Circumference (WC) and Waist to hip Circumference Ratio (WHR). The cross-sectional observational study was conducted in the endemic iodine deficiency areas in Prambanan Sub-district, Sleman Regency. A total subject of 134 women of reproductive age were selected randomly from the source population of 592. Thyroid dysfunction determined by Thyroid Stimulating Hormone (TSH) and Free Thyroxine (FT4) level were measured by ELISA method. Total cholesterol level was measured by colorimetric method using a spectrophotometer. We also measured the weight and height for BMI calculation as well as the WC and Hip Circumference (HC). Chi-Square test was applied to analyze association between thyroid dysfunction with TC levels, BMI, WC and WHR. Results found the percentage of thyroid dysfunction in subjects was 39.6% (hypothyroidism 4.5% and hyperthyroidism 35.1%). The percentage of subjects with hypercholesterolemia was 34.3%. The BMI calculation found that the underweight, overweight and obesity proportions were 6.7%; 16.4% and 27.6% respectively; WC >80 cm was 29.9% and WHR >0.85 was 38.8%. There was no association between thyroid dysfunction and TC levels, BMI and WC ($p>0.05$) respectively. Meanwhile thyroid dysfunction was significantly associated with WHR ($p<0.05$). Therefore, women in reproductive age with thyroid dysfunction should be aware of their increasing abdominal adiposity.

Keywords: body mass index, thyroid dysfunction, total cholesterol levels, waist circumference, waist to hip circumference ratio

INTRODUCTION

Iodine Deficiency Disorder (IDD) decreases quality of life in all age groups, starting from fetus, neonatal, children, adolescents, adults, and elderly (Eastman & Zimmermann 2018). The negative health impact of iodine deficiency includes a very wide spectrum of problem such as miscarriage, stillbirth, congenital defects, prenatal death, fetal death, cretinism, goiter, hypothyroidism, IQ decrease, mental dysfunction, muscle dysfunction, stunted growth, and Iodine Induced Hyperthyroidism (IIH) (Eastman *et al.* 2019). Several problems related to iodine and thyroid dysfunction occur more likely in women than men (Castello & Caputo 2019). Hence, it is recommended that women do regular screening for iodine deficiency, especially for those who are older than 35 years old. The younger the better, to prepare for pregnancy because failed early detection will results in significant risks on fetal death, congenital hypothyroidism, cretinism, mental retardation, psychomotor developmental disorders, and decreased intelligence in infants (Pearce *et al.* 2016; Eastman & Zimmermann 2018).

One of the indicators used to determine the endemicity of iodine deficiency in a region is using the prevalence of Total Goiter Rate (TGR), which is the total prevalence value of enlarged thyroid glands of a population in a region, either it is a grade I (palpable) or grade II (visible) with the threshold of 5% (WHO 2014). The survey result in Prambanan Sub-district, Sleman

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Regency, Yogyakarta, Indonesia showed that TGR in women was 13%. Thus, defined as an endemic area of iodine deficiency (Mutalazimah *et al.* 2013). Severe iodine deficiency is the cause of hypothyroidism, mild to moderate iodine deficiency have a higher prevalence of hyperthyroidism. Hyperthyroidism that occurs in areas of iodine deficiency is caused by IIH mechanism (Ross *et al.* 2016). Furthermore, some studies found the relation of the effect of thyroid dysfunction towards metabolic syndrome with the indicator of hypercholesterolemia, hyperlipidemia, and obesity (Khatiwada *et al.* 2016; Xu *et al.* 2019).

International Diabetes Federation (IDF) defines metabolic syndrome as a cluster of the most dangerous heart attack risk factors: diabetes and raised fasting plasma glucose, abdominal obesity, high cholesterol and high blood pressure (IDF 2007). Obesity could be interpreted by using anthropometric measurement such as Body Mass Index (BMI) and Waist Circumference (WC), which are used as one of the predictor for metabolic syndrome (Wong *et al.* 2021). Similarly, increasing waist circumference (Ross *et al.* 2020) and Waist to Hip Circumference Ratio (WHR) could represent abdominal adiposity when compared to BMI (Mulyasari & Pontang 2018). Previous study also found that WC and WHR can be used for predicting insulin resistance in adolescents (Fitriyanti *et al.* 2019).

Thyroid dysfunction is commonly defined through Thyroid Stimulating Hormone (TSH) level and Free Thyroxine (FT4) level. Thyroid hormone functions to control metabolism and energy homeostatic and influence body weight, thermogenesis, lipolysis, and cholesterol metabolism. Moreover, TSH serves as the receptor in fatty tissue, induces the differentiation of pre-adipocytes become adipocytes and the expansion of adipose tissue (adipogenesis) (Volke & Krause 2021). Thyroid dysfunction is also strongly related to body weight (Ríos-Prego *et al.* 2019). The increase of TSH level with normal level of thyroid hormone concentration shows subclinical hypothyroidism, and it has been constantly found on obese subjects (Ríos-Prego *et al.* 2019; Mahdavi *et al.* 2021).

Thyroid hormones are essential for women reproductive system, through its roles in the metabolism and growth of ovarian, uterine, and placental tissues. This is related to the interaction of the thyroid hormone with multiple reproductive hormones such as estrogen and prolactin. Thyroid dysfunction in women in of reproductive age can caused menstrual irregularity, endometrial disorder, infertility and the risk of causing pregnancy disorders such as uterine growth disorder, pre-eclampsia, miscarriage and premature birth (Silva *et al.* 2018). Therefore, this research aimed to describe thyroid dysfunction based on TSH and FT4 level on women of reproductive age in iodine deficiency endemic areas, which was in Prambanan Sub-district, Sleman Regency, Yogyakarta, Indonesia. In addition, considering the role of thyroid hormone in human metabolism this study also aimed to determine its relationship with total cholesterol levels and anthropometrics status using BMI, WC and WHR as predictors for metabolic syndrome.

METHODS

Design, location, and time

This cross-sectional study was conducted in Gayamharjo, Wukirharjo and Sumberharjo villages in Prambanan Sub-district, Sleman Regency, Yogyakarta, Indonesia from June to September 2018. This research was approved by ethics committee from Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine Universitas Gadjah Mada Yogyakarta with reference number: KE/FK/270/EC. Each respondent has also signed an informed consent form.

Sampling

The target population in this study were all reproductive age women aged 18−45 years in endemic areas of IDD in Prambanan Sub-district of 3,589 women: the villages of Gayamharjo (n=736), Wukirharjo (n=535) and Sumberharjo (n=2,318). This study excluded subjects without contraception (n=714) and taking hormonal contraception (n=2283), therefore the source population who did not use hormonal contraception was 592 women: Gayamharjo (n=92), Wukirharjo (n=132) and Sumberharjo (n=368).

Sample size was calculated from the source population of 592 women using the following formula, $n=Z\alpha^2.P(1-P)/d^2$ ($Z\alpha$ with confidence level 95%=1.96; P, proportion of

TGR in Prambanan Sub-district=0.13; 1-P=0.87; d, relative precision=0.06). From the Sample Size Version 2.0 software it was computed 121 sample, a 10% non-response rate anticipated was using in this study. Thus, the total sample was 134 women and they were selected using computerized simple random sampling by IBM SPSS for Windows Version 23.0. All of those 134 women were assessed by physicians using checklist questionnaire based on signs and symptoms related to severe endocrine disorder and chronic diseases, such as thyroid cancer, thyrotoxicosis, chronic diabetes mellitus, Grave's diseases, chronic cardiovascular disease, chronic emphysema, chronic kidney failure, chronic liver cirrhosis, and various malignancies. None of them had any of those signs and symptoms, therefore all of those 134 women were eligible to participate in this study.

Data collection

Socio-demographic data (age, education level, occupation, family income) were obtained by interview using a questionnaire. The TC levels was measured by colorimetric method using spectrophotometer. Anthropometric assessments in this study using the BMI, WC and WHR were done by trained nutritionist. BMI calculated as weight in kilograms divided by the square of height in meters (kg/m^2), body weight was measured using digital body scale with precision 0.1 kg (Camry, Indonesia), while height was measured using microtoise stature meter 200 cm with precision 0.1 cm (GEA, Indonesia). The WC and HC was measured using measuring tape and stated in centimeters (cm); and the WHR was calculated as WC divided by the HC. Thyroid dysfunction was interpreted from TSH and FT4 levels using ELISA method, trough collecting 7 ml of venous blood sample by professional medical laboratory staff, which was analyzed in Clinical Pathology Laboratory of dr. Sardjito Hospital Yogyakarta.

Data analysis

In this study TC levels were classified as normal if the value <200 mg/dl and high if the value ≥200 mg/dl (Prihantini 2021). BMI data were classified according to Asian criteria: underweight (<18.5kg/m^2), normal weight (18.5 to <23.0 kg/m^2), overweight (23.0 to <25.0 kg/m^2), obesity (≥25 kg/m^2): obesity I (25–29.9 kg/m^2), and obesity II (≥30 kg/m^2) (Pengpid & Peltzer 2017). BMI data were also categorized into abnormal (underweight, overweight, obesity) and normal (normal weight). The WC cut off point of 80 cm for women to identify risk of Type 2 Diabetes Mellitus (T2DM) among Indonesian population (Harbuwono *et al.* 2020) and the WHR cut off point of 0.85 for women to determine risk of metabolic syndrome (Adegoke *et al.* 2021).

Thyroid function is defined through the measurement result of Thyroid Stimulating Hormone (TSH) and Free Thyroxine (FT4). Conventional reference intervals for TSH and FT4 were 0.4−4.0 mIU/l (Razvi *et al.* 2020) and 0.8–1.8 ng/dl (Aubert *et al.* 2017), respectively. Based on the reference interval, thyroid function is divided into two groups, namely the thyroid dysfunction group and the normal thyroid function group. Thyroid dysfunction was defined as: (1) subclinical hypothyroidism, if TSH level above reference interval, with FT4 was still in the normal reference range; (2) clinical hypothyroidism was indicated by the increase of TSH and the decrease of FT4; (3) subclinical hyperthyroidism if TSH level below reference value, with FT4 was still in the normal reference interval; (4) clinical hyperthyroidism was indicated by the decrease of TSH and the increase of FT4. Meanwhile the normal thyroid function if both TSH and FT4 were still in the normal reference interval (Arce-Sánchez *et al.* 2021). In this study, thyroid dysfunction was classified as "Yes" (for subjects with subclinical hypothyroidism, clinical hypothyroidism, subclinical hyperthyroidism, and clinical hyperthyroidism) and "No" (for subject with normal thyroid function).

IBM SPSS Statistic for Windows Version 23.0 (IBM Corp, Armonk, New York, US) was used to process and analyze data. Univariate analysis was carried out by describing all categorical data in terms of frequency and percentage, while numerical data was described by presenting mean and Standard Deviation (SD) for normal distribution data, and presenting median and range for non-normal distribution data. Numerical data analyzed for normality were TSH, FT4, total cholesterol, BMI, WC and WHR. TSH was not normally distributed, therefore descriptive analysis used the median and range, meanwhile other data that were normally distributed described using the mean and SD. Association of thyroid dysfunction, total

cholesterol levels and anthropometry (BMI, WC and WHR) was analyzed using Chi-Square test. A threshold of $p<0.05$ was set as significance level.

RESULTS AND DISCUSSION

Socio-demographic characteristics of subjects

Socio-demographic data described and analyzed were age, educational level, occupation, and family income (Table 1).

Table 1 shows that this study found the percentage of women who were at risk for reproductive problem based on age was 37.3%. Overall, the educational level of respondents was still relatively low, namely 3.0% illiterate and 25.4% with elementary school. This study, which was conducted in the mountainous area, found that most women were mostly housewife (51.5%) and the second most common occupation was farmer (26.9%). This study found 90.3% of subjects had a monthly family income below the Sleman Regency regional minimum wage in 2018 (IDR 1,574,550.00 or $109).

Thyroid function in subjects

The interpretation of TSH and FT4 level as the indicator of thyroid dysfunction defined by normal reference interval of 0.4−4.0 mIU/l and 0.8−1.8 ng/dl, respectively. The median (range) for TSH was 0.59 (0.004−22.4) mIU/l and the mean FT4 level was 0.99±0.27 ng/dl. For the thyroid function categorization, TSH could not stand alone, it needs to be interpreted simultaneously with FT4 level. The description of the thyroid function in subjects are presented in Table 2.

We found 39.6% of all subjects had thyroid dysfunction, where 35.1% was in the form of hyperthyroidism and 4.5% suffered from hypothyroidism. (Table 2). Previous study in Magelang Regency, Central Java found

Table 1. Socio-demographic characteristics of subjects

Variables	n (%)
Age (year)	
At risk from reproductive problems (<20 or >35)	50 (37.3)
Not at risk from reproductive problems (20−35)	84 (62.7)
Mean±SD of age (year)	33.81±7.09
Education	
Unschooling	4 (3.0)
Elementary school	34 (25.4)
Junior high school	44 (32.8)
Senior high school	45 (33.6)
University	7 (5.2)
Occupation	
Housewife	69 (51.5)
Farmer	34 (26.9)
Merchant	2 (1.5)
Private employee	24 (17.9)
Government employee	3 (2.2)
Family income (IDR)	
<Minimum regional wage (1,574,550.00)	121 (90.3)
≥Minimum regional wage (1,574,550.00)	13 (9.7)
Mean±SD of family income (IDR)	729,477±456,828

IDR: Indonesian Rupiah; SD: Standart Deviation

Table 2. Thyroid function in subjects

Variables	n (%)
Thyroid function	
Thyroid dysfunction	53 (39.6)
Subclinical hypothyroidism	2 (1.5)
Clinical hypothyroidism	4 (3.0)
Subclinical hyperthyroidism	45 (33.6)
Clinical hyperthyroidism	2 (1.5)
Normal thyroid function	81 (60.4)
Thyroid dysfunction status	
Yes	53 (39.6)
No	81 (60.4)
TSH level (mIU/l)	
Median (range) of TSH level (mIU/l)	0.59 (0.004-22.4)
FT4 level (ng/dl)	
Mean±SD of FT4 level (ng/dl)	0.99±0.27

TSH: Thyroid Stimulating Hormone; FT4: Free Thyroxine; SD: Standart Deviation

lightly higher prevalence which was 39.8% (Nurcahyani *et al.* 2020). The higher prevalence of hyperthyroidism than hypothyroidism in IDD endemic areas might be caused by Iodine Induced Hyperthyroidism (IIH). This often associated with the use of iodine prophylaxis such as excess of iodine supplementation, high iodine-containing drugs consumption and frequent consumption of iodine fortified food (Mutalazimah *et al.* 2013). The percentage of clinical hypothyroidism and hyperthyroidism in this study were similar the epidemiology report, which found that the prevalence of clinical hypothyroidism was approximately 1–2%. Similarly, it was reported that the prevalence of clinical hyperthyroidism was 0.5–2%. Meanwhile, the percentage of subclinical hypothyroidism in this study was lower than the findings of National Health and Nutrition Examination Survey (NHANES III), ranging between 4 and 21%. However, the percentage of subclinical hyperthyroidism in this study was higher than the results of a mini review in some surveys conducted in Indonesia, which found that hyperthyroidism was 6.9% (Miharja & Karyana 2019).

Hyperthyroidism was often found in IDD endemic areas this could happen through the mechanism of Autonomous Functioning Thyroid Nodule (AFTN). This mechanism is a biological fundamental reason for hyperthyroidism, often caused by mutation of thyroid cells which causes the autonomous function. Another cause of hyperthyroidism on subjects with iodine deficiency is family history of autoimmune condition, inherited from parents through thyroid-specific genes mechanism, similar to TSH receptor (TSHr) and Thyroglobulin (Tg), which loses its responsibility and causing unwarranted feedback mechanism disorders of the thyroid hormone (Stefan & Faustino 2017). Even though most of them are considered subclinical, it is possible to develop into overt or secondary disorder phase, if it is not anticipated with adequate intervention.

Total cholesterol levels, BMI, WC and WHR in subjects

The mean of total cholesterol levels, WC and WHR was still in normal category. Meanwhile, the mean BMI was in the overweight category. The mean/median and category of total cholesterol levels, BMI, WC, and WHR are presented Table 3.

This study found that more than one third (34.3%) of subjects had total cholesterol

Table 3. Total cholesterol levels and anthropometric status (BMI, WC, and WHR) in subjects

Variables	n (%)
Total Cholesterol levels (mg/dl)	
Hypercholesterolemia (>200)	46 (34.3)
Normal (≤200)	88 (65.7)
Mean±SD of total cholesterol (mg/dl)	177.21±39.58
BMI	
Underweight (<18.5)	9 (6.7)
Normal (18.5−22.9)	66 (49.3)
Overweight (23.0−24.9)	22 (16.4)
Class I Obesity (25.0−29.9)	26 (19.4)
Class II Obesity (>30.0)	11 (8.2)
Mean±SD of BMI	23.40±3.99
WC (cm)	
At risk from abdominal obesity (>80)	40 (29.9)
Not at risk from abdominal obesity (≤80)	94 (70.1)
Mean±SD of WC (cm)	75.92±8.88
WHR	
At risk from abdominal obesity (>0.85)	52 (38.8)
Not at risk from abdominal obesity (≤0.85)	82 (61.2)
Mean±SD of WHR	0.82±0.06

BMI: Body Mass Index; WC: Waist Circumference; WHR: Waist to Hip Ratio; SD: Standard Deviation

levels of >200 mg/dl or suffered from hypercholesterolemia; this is an increasing concern considering the fact that the subjects lived in rural mountainous area. It was assumed that they were not exposed to the risk factors of hypercholesterolemia such as fast food or food with high cholesterol level. This prevalence was higher compared to a study conducted by Nurcahyani *et al.* (2020) in IDD clinic of research and development center Magelang, Central Java, Indonesia which was 21.7%. This study found 44.0% of subjects were overweight or obese and 6.7% was underweight. This was higher than the previous study which was 38.6% (Nurcahyani *et al.* 2020). We found 38.8% of subjects with WHR of >0.85, which was included in the category of at risk towards abdominal adiposity. Hence, this study add to the evidence that the risk of obesity did not only threaten to modern community in urban areas, but also to the rural community in mountainous areas. However, the prevalence was lower than a previous study in Iran which found that 68.67% of women with WHR of >0.85 (Shahvazi *et al.* 2017).

Association of thyroid dysfunction, total cholesterol levels and anthropometric status (BMI, WC and WHR)

The association between thyroid dysfunction and total cholesterol levels, BMI, WC and WHR were tested using Chi-Square test as shown in Table 4.

Table 4. Association of thyroid dysfunction, TC, BMI, WC, and WHR

	Thyroid dysfunction	Potential risks		p
		n	%	
Hypercholesterolemia	Yes	16	30.2	0.414
	No	30	37.0	
Non hypercholesterolemia	Yes	37	69.2	
	No	51	63.0	
BMI abnormal	Yes	30	56.6	0.273
	No	38	46.9	
BMI normal	Yes	23	43.4	
	No	43	53.1	
WC at risk	Yes	18	34.0	0.400
	No	22	27.2	
WC not at risk	Yes	35	66.0	
	No	59	72.8	
WHR at risk	Yes	15	28.3	0.044
	No	37	45.7	
WHR not at risk	Yes	38	71.7	
	No	44	54.3	

BMI: Body Mass Index; TC: Total Cholesterol Level; WC: Waist Circumference; WHR: Waist to Hip Ratio

Chi-Square test showed that there was no significant relationship between thyroid dysfunction, TC, BMI and WC (p=0.414; p=0273; p=0.400) respectively. The findings were in line with previous studies conducted in China, in which they found no significant relation between TSH and total cholesterol, as well as TSH and BMI (Xu *et al.* 2019). The most fundamental factor that determined the relevance with previous studies was the existence of other factors as driving factors in the occurrence of metabolic syndrome, which were not studied in this research such as age, dietary pattern, and activity pattern. There was also another determining factor in a study conducted in China with samples that were predetermined as patients with Coronary Heart Disease (CHD); whereas, in this research, the metabolic syndrome condition of each sample was not known in advance. The previous study discovered there is a significant relationship between TSH changes and alterations of WC in women in Iran (Motamed *et al.* 2016).

Our study found that thyroid dysfunction was associated with WHR (p=0.044). TSH through receptor in fatty tissue induced the differentiation of pre-adipocytes to become adipocytes and the expansion of adipose tissue (adipogenesis). The increase of TSH level with normal concentration level of thyroid hormone showed subclinical hypothyroidism had been consistently found in obese subjects. The production of TSH was also regulated by neurotransmitter and hormone that affected body weight such as neuro peptide and alpha melanocyte stimulating hormone that were bound by peptides and connected with hypophysiotropic hormone namely Thyrotropin Releasing Hormone (TRH) neurons. The neurotransmitter and hormone were also affected by leptin. TSH also directly induced the synthesis and release of adipokines, in which some of the

adipokines functioned to control appetite through regulatory mechanisms in the brain (Volke & Krause 2021). Hence, TSH is related to the pattern of appetite and induces adipocyte tissue; therefore, it is related to the measurable weight changes reflected in WHR.

CONCLUSION

This study found clinical and subclinical thyroid dysfunction, both hypothyroidism and hyperthyroidism in women of reproductive age living in IDD endemic area. Thyroid dysfunction had significance association to WHR. Thus, awareness of nutritional status, particularly WHR indicator is important for this demography. WHR reflects the accumulation of abdominal adiposity, thus efforts to reduce the risk of high WHR in women reproductive age with thyroid dysfunction should include maintaining a balanced diet and doing regular physical activity. Follow up studies with better design such as case control or cohort approach are pivotal. It is also important to utilized a more complete markers for metabolic syndrome which include all lipid profiles (LDL, HDL, and triglyceride).

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DECLARATION OF INTERESTS

The authors confirm that there are no known conflicts of interest related with this paper. All authors have made substantial contributions in the study and manuscript writing.

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