# Association of Thyroid Function with Metabolic Parameter in IDD Clinic Patients, Magelang Research and Development Center

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## Abstract

Metabolic parameters, such as lipid and glucose metabolism, blood pressure, and body weight, are influenced by thyroid hormones. Thyroid dysfunction may lead to the development of the metabolic syndrome. The study aimed to analyze the relationship between thyroid dysfunction and metabolic parameters in IDD clinic patients, Magelang Research and Development Center. A cross-sectional study of 83 patients who met the inclusion and exclusion criteria. Total cholesterol, LDL, HDL, TSH, and free T4 concentration had been measured in all subjects. BMI and blood pressure were measured. Concentrations of lipids, triglycerides, free T4, and TSH were analyzed. The mean age of the patient was 33.5 ± 8.6 of whom 6 (7.2 %) subclinical hypothyroidism, 17 (20.5 %) overt hyperthyroidism, and 17 (20.5 %) had subclinical hyperthyroidism. There was positive relationship between TSH and systolic; whereas, FT4 was associated with BMI, systole, and diastole after adjustment for age. Overt hyperthyroidism had significantly higher odds of hypertension after adjustment for age and BMI (OR 5.557 (1.310-23.578), $p<0.05$). Hyperthyroidism may induce hypertension.

***Keywords :*** *thyroid function, triglycerides, lipid, blood pressure*

## Introduction

Thyroid hormone plays a important role in glucose[1] and lipid metabolism[2], blood pressure[3]and body weight[4], as it regulates energy metabolism and thermogenesis. All of them are related with various metabolic parameters. Thyroid dysfunction may lead to the development of metabolic syndrome[1],[5]. The occurrence of dyslipidemia, increased blood pressure, increased fasting blood glucose levels, and abdominal obesity is some of the risk factors for metabolic syndrome[6].

Research has shown that thyroid hormones directly and indirectly impact the cardiovascular system[7] and especially hypertension[8]. Patients with thyroid diseases, such as hyperthyroidism, often have signs and symptoms of cardiovascular changes, leading to increased cardiac output and hypertension (cardiac arrhythmias, hypercoagulopathy, stroke, and pulmonary embolism). In the hyperthyroid patient, systolic blood pressures had usually elevated, but not in diastolic blood pressures[9]. Overt hypothyroidism causes an elevate in blood pressure and lipid[10].

Metabolic syndrome and thyroid dysfunction are very common endocrine disorders and are associated with various metabolic aspects, morbidity and mortality[11]. The metabolic syndrome may increase in hypothyroidism or subclinical hypothyroidism. Both together have a major impact on individual health regarding cardiovascular and metabolic risk factors, especially in the elderly[5]. Therefore, the aim of this study was to evaluate the association of thyroid dysfunction with metabolic parameter in a patient with a goiter who came to the IDD clinic of Magelang Research and Development Center (R&DC).

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## Method

We conducted a cross-sectional study on IDD clinic patients, Magelang Research and Development Center during 2018. The study was nested within the principal study focused to evaluate the relationship between thyroid functions and lipid profiles in women of childbearing age with goiter[12]. We excluded patients if they had complications from other metabolic diseases such as diabetes mellitus (DM). The ethics committee of the Islamic University of Indonesia approved the protocol for this study. The minimum sample estimate required is 83 samples, using a diagnostic test with 95% CI and 95% test power[13]. Data and sample characteristics were collected by questionnaire-based interviews. Data collection on physical indicators, health status, and disease history were carried out by clinical examination by an experienced doctor. Nutritional status (height, weight) was determined and collected anthropometry by measuring height using Microtoise and weighing it using Seca digital scale.

Biochemical indicator data including TSH, free-T4 (fT4), LDL, HDL, and total cholesterol were obtained by taking blood without fasting from the veins as much as 3.5 ml according to procedures taken by the health analyst. The blood was rotated at 3000 rpm for 10 minutes to be separated between plasma and serum. The resulting serum was divided into 5 tubes for the examination of TSH, fT4, LDL, HDL, and total cholesterol. The serum was stored in a freezer at -20o C before analysis. The analysis of TSH, fT4, LDL, HDL, and total cholesterol used the ELISA method.

TSH reference range 0.31–2.50 mIU and no thyroid medication was defined as euthyroid. Other thyroid test results such as TSH> 2.50 and 0.80 ≤ FT4 ≤ 2.00 are considered subclinical hypothyroidism; TSH> 2.50 and FT4 <0.80 for real hypothyroidism; TSH <0.30 and 0.80 ≤ FT4 ≤ 2.00 as subclinic hyperthyroidism; and TSH <0.30 and FT4> 2.00 as overt hyperthyroidism[14]. The criteria for hypertension were defined according to the Joint Interim Statement (JIS) as systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg while not taking any hypertension medication[15]. Decrease in HDL-C as determined by serum HDL-C <40 mg / dl in men and <50 mg / dl in women or on special medication. Hypertriglycerdeemia is determined by serum triglycerides ≥ 150 mg / dl or by specific treatment. Hypercholesterolemia is determined by serum LDL-C> 100 mg / dl and hypercholesterolemia is determined by total serum cholesterol> 200 mg / dl.

Characteristics and laboratory data of patients are presented as mean ± SD for normal distribution variables and median (min-max) for non normal distribution variables. Data were compared between different groups of thyroid function, using ANOVA or Kruskal Wallis based on variables distribution. Linear regression was used to calculate the correlation between serum TSH and FT4 values with metabolic variables. The effect of related variables on the dependent variable was evaluated using the nonstandard coefficient β. Chi-square test was used to compare cases of metabolic variables between different thyroid function groups. Multivariate logistic analysis was used to calculate the odds of case metabolic variables adjusted for age and BMI; and evaluate the association between thyroid dysfunction and metabolic variables. Data analysis was performed using SPSS 22.0 software with a statistical significance value of p-values <0.05.

## Result

**Table 1. Characteristics of the patients by thyroid function grup.**

| | **Euthyroid (N=43)** | **Overt hyperthyroidism (N=17)** | **Subclinical hyperthyroidism (N=17)** | **Subclinical hypothyroid (N=6)** |
|---|---|---|---|---|
| Age (years) | 34.6 ± 8.24 | 31.6 ± 8.19 | 34.5 ± 9,37 | 27.5 ± 9.31 |
| Weight (kg) | 54.4 ± 9.13 | 45.9 ± 5.96 | 51.4 ± 10.18 | 50.7 ± 9.37 |

***Cont...*** **Table 1. Characteristics of the patients by thyroid function grup.**

| | | | | |
|---|---|---|---|---|
| BMI (kg/m2) | 23.4 ± 3.74 | 20.1 ± 2.52** | 21,8 ± 4.34 | 22.3 ± 5.78 |
| Total cholesterol (mg/dl) | 186.8 ± 33.71 | 119.9 ± 19.04*** | 171,6 ± 20,71* | 210,3 ± 41,54 |
| HDL-C (mg/dl) | 53.4 ± 8.55 | 47.6 ± 9.35* | 57,3 ± 10.09 | 53.5 ± 8.89 |
| LDL-C (mg/dl) | 122.1 ± 28.42 | 62.1 ± 16.64*** | 104.2 ± 16.94* | 128.7 ± 36.26 |
| Triglyceride (mg/dl) | 109.4 ± 62.23 | 89.0 ± 24.01 | 90.6 ± 27.34 | 127.0 ± 67.42 |
| Systolic BP (mmHg) | 122.9 ± 17.47 | 135.8 ± 20.00* | 130.2 ± 27.43 | 124.2 ± 30.59 |
| Diastolic BP (mmHg) | 77.6 ± 11.28 | 77.4 ± 10.92 | 78.9 ± 17.88 | 75.5 ± 11.62 |
| fT4 (ng/L) | 1.16 ± 0.25 | 6.25 ± 1.66*** | 1.26 ± 0.35 | 0.92 ± 0.48 |
| TSH (mIU/l) | 1.36 ± 0.65 | 0.03 ± 0.01*** | 0.08 ± 0.09*** | 3.56 ± 1.27*** |

Values are presented as mean ± SD ; p_Values are for comparison with euthyroid subject; $p<0.05$; ** $p<0.01$; *** $p<0.000$

Mean age of patients (n = 83) was 33.5 ± 8.6; 43 (51.8%) of the participant were euthyroid, 6 (7.2 %) subclinical hypothyroidism, 17 (20.5 %) overt hyperthyroidism, and 17 (20.5 %) had subclinical hyperthyroidism. There were significant differences in BMI, total cholesterol, LDL-C, HDL, LDL, systolic, fT4, and TSH between overt hyperthyroid subjects and the euthyroid group. Subclinical hyperthyroid patients had significantly lower total cholesterol, LDL, and TSH values than the euthyroid group (Table 1). Subclinical hypothyroid patients had significantly higher values of TSH than the euthyroid group. There was positive associations for TSH with systolic by linear regression analysis; the significance had disappeared after adjusted for age and M BMI. FT4 had associated with BMI, systolic, and diastolic after adjustment for age (Table 2).

**Table 2. Association of thyroid hormones levels with lipid and blood pressure parameter.**

| **N=83** | **Model** | **TSH (mIU/l)** | | | **fT4 (ng/dl)** | | |
|---|---|---|---|---|---|---|---|
| | | **β** | **R2** | **p-Value** | **β** | **R2** | **p-Value** |
| BMI (kg/m2) | 1 | 0.729 | 0.531 | 0.100 | 0.500 | 0.250 | 0.313 |
| | 2 | 1.144 | 0.589 | 0.219 | 1.802 | 0.817 | 0.035* |
| Total cholesterol (mg/dl) | 1 | 0.749 | 0.561 | 0.087 | 0.201 | 0.040 | 0.703 |
| | 2 | 0.649 | 0.609 | 0.200 | 0.214 | 0.041 | 0.753 |
| HDL-C (mg/dl) | 1 | 0.002 | 0.000 | 0.997 | 0.348 | 0.121 | 0.500 |
| | 2 | 0.474 | 0.406 | 0.455 | 0.589 | 0.227 | 0.419 |
| LDL-C (mg/dl) | 1 | 0.565 | 0.320 | 0.242 | -0.080 | 0.006 | 0.881 |

***Cont...*** **Table 2. Association of thyroid hormones levels with lipid and blood pressure parameter.**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 | 0.521 | 0.320 | 0.644 | -0.588 | 0.079 | 0.654 |
| Triglyceride (mg/dl) | 1 | 0.261 | 0.068 | 0.617 | 0.005 | 0.000 | 0.992 |
| | 2 | -0.138 | 0.271 | 0.847 | -0.056 | 0.005 | 0.947 |
| Systolic BP (mmHg) | 1 | 0.735 | 0.541 | 0.096 | 0.565 | 0.320 | 0.242 |
| | 2 | 0.980 | 0.569 | 0.239 | 1.618 | 0.844 | 0.028* |
| Diastolic BP (mmHg) | 1 | 0.830 | 0.689 | 0.041* | 0.660 | 0.435 | 0.154 |
| | 2 | 0.977 | 0.708 | 0.121 | 1.323 | 0.823 | 0.034* |

*p<0.05; Model 1 : Crude ; Model 2 : Adjusted for age

The proportion of hyper-cholesterolemia (0.0%) and hyper LDL-C (0.0%) were significantly lower in patients with overt hyperthyroidism than in other groups ($p < 0.05$). A significant odds ratios for proportion hypertension was observed only in overt hyperthyroidism (OR: 5.557, 95% CI: 1.310-23.578, p=0.020) (Table 3).

**Table 3. Comparison of cases of metabolic variables in thyroid function groups.**

| | **Model** | **Euthyroid** | **Overt hyperthyroidism** | | **Subclinical hyperthyroidism** | | **Subclinical hypothyroidism** | |
|---|---|---|---|---|---|---|---|---|
| | | **%cases** | **%cases** | **OR (95% CI)** | **%cases** | **OR (95% CI)** | **%cases** | **OR (95% CI)** |
| Hyper-triglycemia | 1 | 18.6 | 0.0 | NA | 0.0 | NA | 33.3 | 2.188 (0.339-14.095) |
| | 2 | | | NA | | NA | | 3.543 (0.373-33.650) |
| Hyper cholesterolemia | 1 | 30.2 | 0.0* | NA | 11.8 | 0.308 (0.061-1.543) | 50.0 | 2.308 (0.410-12.985) |
| | 2 | | | NA | | 0.328 (0.063-1.699) | | 3.067 (0.462-20.342) |
| Reduced HDL-C | 1 | 27.9 | 47.1 | 2.296 (0.718-7.342) | 23.5 | 0.795 )0.216-2.928) | 50.0 | 2.583 (0.456-14.623) |
| | 2 | | | 3.358 (0.928-12.143) | | 0.940 (0.246-3.601) | | 2.880 (0.453-18.312) |
| Hyper LDL-C | 1 | 76.7 | 0.0*** | NA | 70.6 | 0.727 (0.206-2.565) | 83.3 | 1.515 (0.158-14.529) |
| | 2 | | | NA | | 0.719 (0.192-2.688) | | 2.117 (0.206-21.778) |
| Hipertension | 1 | 38.1 | 56.3 | 2.089 (0.650-6.716) | 29.4 | 0.677 (0.201-2.282) | 33.3 | 0.813 (0.133-4.955) |
| | 2 | | | 5.557 (1.310-23.578)* | | 0.690 (0.172-2.769) | | 2.112 (0.193-23.173) |

P-Values are for comparison with euthyroid subject : * p<0.05; ***p<0.000; Model 1 : Crude ; Model 2 : Adjusted for age and BMI

## Discussion

This study showed that overt hyperthyroidism is associated with a higher risk of hypertension. In hyperthyroid patients, systolic blood pressure is usually elevated, not diastolic blood pressure[9]. Thyroid hormones have a direct and indirect cellular effect on the cardiac-renal-vascular system[8]. Excess T3 causes tachycardia, diminished systemic vascular, increased cardiac preload and ventricular contractility[16], resulting in increased cardiac output and hypertension[8]. The results of a study in Hong Kong stated that 591 patients with hyperthyroidism, 9% were accompanied by hypertension, and the prevalence of heart failure was higher in patients with hypertension[17]. Hyperthyroidism caused high cardiac output and increased heart rate, decreased peripheral vascular resistance, and circulatory hyperdynamics. This condition results in increased sodium absorption and blood volume due to decreased renal perfusion pressure and activation of the angiotensin-aldosterone axis[8].

The thyroid gland makes hormones (T4 and T3), and the synthesis of the hormone thyroid is regulated by TSH. Thyroid hormone is transported across the cell membrane and regulate gene expression by binding thyroid hormone receptors to provide genomic and nongenomic effects[18]. Thyroid hormone disruption will result in inhibition of gene expression including the cellular signaling pathway of gluconeogenesis, lipogenesis, insulin signaling, and adenylate cyclase signaling. The non-genomic effect associated with thyroid hormones will cause changes in the cell membranes and cytoplasm include regulation of mitochondrial metabolism, increased glucose uptake, regulating ion pump concentrations on cell membranes, regulation of lipid metabolism in the liver, and heart rate control[19].

The hyperthyroid group was significantly lower in total cholesterol, HDL-C, and LDL-C than in the euthyroid group (Table 1). The subclinical hypothyroidism group had higher lipid levels than euthyroid; it's not that different. The thyroid hormone plays an important role during the transport of lipoproteins[2]. Excess thyroid hormone may increase the induction of coenzyme 3-hydroxy-3-methyl-glutaric-CoA reductase (HMG-CoA reductase) in the liver by stimulating cholesterol synthesis so that cholesterol levels decrease. Thyroid hormones also control the sterol regulator element-binding protein-2 (SREBP-2) which regulates the expression of low-density lipoprotein (LDL) receptors. Cholesteryl ester transfer protein (CETP) had influenced by thyroid hormone, which functions to stimulate the conversion of HDL to very-low-density-lipoprotein (VLDL) in the liver[10].

We found significant positive associations of free T4 with BMI systole and diastole after adjusted for age. High levels of circulating thyroid hormones in the body alter the levels of several other hormones and peptides which have potential effects on blood pressure. Some studies have reported hyperthyroidism can increase levels of endothelin-1 and its receptor. Endothelin-1 can induce hypertension through a direct effect on blood vessel tone, causes salt and water retention, and patient with salt-sensitive hypertension have high levels[9]. Increased endothelin-1 in the atrial increases the risk of atrial fibrillation by promoting atrial inflammation, remodeling, and cardiac myocyte hypertrophy. The development of atrial fibrillation in a patient with hyperthyroidism had associated with endothelin-1, independent of age[20]. Besides, there is increased arterial stiffness and upregulation of erythropoietin synthesis at high T3 levels, resulting in increased intravascular volume. These changes create a hyperdynamic state with a cardiac output of 50-300 percent higher than those in normal[9].

After adjusting for age, there was a significant positive association between free T4 and BMI, systole, and diastole. High levels of circulating thyroid hormone in the body have a possible effect on blood pressure. Overt hyperthyroidism can increase the endothelin-1 level and its receptors resulting in vascular tone, leading to salt and water retention, and an increase in blood pressure[9]. The risk of atrial fibrillation increases with the increase in endothelin-1 in the atria. The development of atrial fibrillation in patients with hyperthyroidism had associated with endothelin-1, independent of age[20]. Besides, there is increased arterial stiffness and upregulation of erythropoietin synthesis at high T3 levels, resulting in increased intravascular volume; 50-300 percent higher than euthyroid[9].

It had estimated that the prevalence of thyrotoxicosis patients with hypertension is around 20-68%[21]. Hyperthyroid patients, elderly, have a higher risk of developing high blood pressure than younger hyperthyroid patients or non-hyperthyroid patients of the same age range[9]. Compared with essential hypertension, the diagnosis of hypertension due to hyperthyroidism is accompanied by other symptoms of hyperthyroidism, such as tachycardia, anxiety or weight loss[22]. Several studies have shown that hyperthyroid patients are more likely to experience a blunt drop in blood pressure at night, which is at risk of causing target organ damage due to hypertension[21].

## Conclusion

This study shows that hyperthyroidism is associated with a higher risk of hypertension. It is necessary to examine hyperthyroidism in patients with hypertension, especially in older patients. So that the diagnosis of thyrotoxicosis can be made early even though elderly hypertensive patients have very mild symptoms of hyperthyroidism.

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