JKKI
SCIENTIA EST BASIC VITAE

Jurnal Kedokteran dan Kesehatan Indonesia

Indonesian Journal of Medicine and Health

Journal homepage: https://journal.uii.ac.id/JKKI

Relationship between thyroid hormone and lipid profile in patients with struma at the iodine deficiency disorder (IDD) clinic of research and development center Magelang

Yusi Dwi Nurcahyani*[1], Prihatin Broto Sukandar[1], Raden Edi Fitriyanto[2], Syaefudin Ali Akhmad[2]
[1]Health Research and Development Center, Magelang, Indonesia
[2]Department of Biochemistry, Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia

Original Article

ARTICLE INFO

Keywords:
lipid profiles,
thyroid dysfunction,
women of childbearing age,
IDD

***Corresponding author:**
youseedn@gmail.com

DOI: 10.20885/JKKI.Vol11.Iss2.art5

History:
Received: October 9, 2019
Accepted: August 10, 2020
Online: August 31, 2020

ABSTRACT

Background: Relationship between thyroid hormones and lipid profiles in patients with struma is a common condition found in IDD endemic areas.

Objective: This study observes relationships between thyroid functions and lipid profiles in woman patients of childbearing age with struma.

Methods: This paper is a cross-sectional study of 83 subjects/patients who met inclusion and exclusion criteria in this study. Total cholesterol, LDL, HDL, TSH, and free T4 concentration were measured in all the patients. Lipid concentrations in patients with thyroid dysfunction and patients with euthyroid were compared by using a linear regression model.

Results: Total cholesterol, LDL, and HDL was significantly lower in patients with primary hyperthyroidism (N=19) than in patients with euthyroid (N=48) (mean±SD 122.8±20.09 mg/dl vs 187.3±33.66 mg/dl, p=0.000 unadjusted, p= 0.000 adjusted for age and BMI); (63.5±16.33 mg/dl vs 121.7±29.71 mg/dl, p=0.000 unadjusted, p= 0.000 adjusted for age and BMI); (48.8±9.66 mg/dl vs 53.6±8.49 mg/dl, P=0.049 unadjusted, p=0.026 adjusted for age and BMI. Serum total cholesterol and LDL was lower in patients with subclinical hyperthyroidism (N= 14) than in patients with euthyroid (N=48), but it was not statistically significant (181.6±32.07 mg/dl vs 187.3±33.66 mg/dl, p=0.577 unadjusted, P=0.719 adjusted for age and BMI); (110.5±14.83 mg/dl vs 121.7±29.71 mg/dl, p=0.181 unadjusted, p=0.250 adjusted for age and BMI). Serum HDL was similarly elevated in patiemts with subclinical hypothyroidism (N=14) than in patients with euthyroid (N=48), but it was not statistically significant (57.4±11.04 mg/dl vs 53.6±8.49 mg/dl, p=0.185 unadjusted, p=0.229 adjusted for age and BMI).

Conclusion: Serum total cholesterol, LDL and HDL was significantly lower in patients with primary hyperthyroidism, but it was not significant for subclinical hyperthyroidism.

Latar Belakang: *Hubungan antara hormon tiroid dan profil lipid pada pasien struma menarik untuk dikaji karena struma adalah kondisi yang biasa ditemui pada daerah endemis gangguan akibat kekurangan iodium (GAKI) dan hal tersebut belum banyak diteliti.*

Tujuan: *Penelitian ini melihat hubungan fungsi tiroid dan profil lipid pada pasien struma wanita usia subur di klinik litbang GAKI.*

Metode: *Penelitian observasional potong lintang pada 83 subyek yang memenuhi kriteria inklusi dan*

eksklusi. Pengambilan darah dilakukan untuk memeriksa kadar kolesterol total, LDL dan HDL, T4 dan TSH. Profil lipid pada sebyek gangguan tiroid akan dibandingkan dengan pasien eutiroid menggunakan regresi linier.

Hasil: *Kolesterol total, LDL, HDL pada subyek hipertiroid primer (N=19) lebih rendah dibanding subyek eutiroid (N=48) dan signifikan secara statistik (rerata±SD 122.8±20.09 mg/dl vs 187.3±33.66 mg/dl, p=0.000, setelah memperhitungkan umur dan IMT p=0.000); (63.5±16.33 mg/dl vs 121.7±29.71 mg/dl, p=0.000, setelah memperhitungkan umur dan IMT p=0.000); (48.8± 9.66 mg/dl vs 53.6 ± 8.49 mg/dl, p=0.049, setelah memperhitungkan umur dan IMT p=0.026). Subyek dengan hipertiroid subklinik (N=14) kadar kolesterol total dan LDL lebih rendah walaupun tidak signifikan (181.6±32.07 mg/dl vs 187.3±33.66 mg/dl, p=0.577, setelah memperhitungkan umur dan IMT p=0,719); (110.5±14.83 mg/dl vs 121.7±29.71 mg/dl, p=0.181, setelah memperhitungkan umur dan IMT p=0.250). Sedangkan kadar HDL pada subyek dengan hipertiroid subklinik lebih tinggi dibanding subyek eutiroid (57.4 ± 11.04 mg/dl vs 53.6 ± 8.49 mg/dl, p=0.185, setelah memperhitungkan umur dan IMT p=0.229).*

Kesimpulan: *Kadar kolesterol total, LDL dan HDL signifikan lebih rendah pada subyek hipertiroid primer tetapi tidak signifikan pada hipertiroid subklinik.*

INTRODUCTION

Thyroid gland hyperplasia is an enlargement of a gland due to a compensatory mechanism of decreasing levels of thyroid hormones that subsequently stimulate thyroid-stimulating hormones (TSH) in the body. It is the most common manifestation of iodine deficiency in children and adults and is often called as struma or goiter.[1-3] This condition may impose risks of hyperthyroidism due to an increase of iodine intakes although within a normal range of consumption.[4]

Thyroid dysfunction can cause a disruption of thyroid hormone production, a catabolic hormone that regulates various metabolic processes, including a lipid metabolism. Thyroid hormones are crucial in maintaining a cholesterol reservoir by regulating important steps of cholesterol synthesis, uptake, and metabolism.[5,6] The disruption of balance between a thyroid hormone and a lipid metabolism can be seen in patients with thyroid dysfunction. The hypothyroid condition can cause an increase of cholesterol and triglyceride levels, whereas hyperthyroidism can cause a decrease of lipid levels.[7] Recent studies show that this condition may extend to subclinical hypothyroid/hyperthyroid ranges, additional evidences for thyroid hormones; meanwhile the TSH exerts an independent effect on lipid metabolism.[7]

The thyroid hormone stimulates the cholesterol synthesis by inducing coenzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) in the liver. Gene expression of low-density-lipoprotein (LDL) receptor is also regulated by the thyroid hormone by controlling the sterol regulatory element-binding protein-2 (SREBP-2). The thyroid hormone can influence high-density-lipoprotein (HDL) metabolism by increasing activities of cholesteryl ester transfer protein (CETP) that functions to regulate the conversion of HDL to very-low-density-lipoprotein (VLDL) in the liver so that the rate of HDL conversion increases.[5,7,8]

The thyroid enlargement has been used in the most endemic struma in epidemiological studies and is still recommended as an indicator to determine endemic areas of iodine deficiency disorder (IDD) on the thyroid hormones. It can directly or indirectly affect blood pressures, lipid metabolisms, and blood glucose.[9] The relationship between the thyroid hormones and the lipid profiles in patients with struma is interesting to study because it is commonly found in endemic areas of IDD but it is lack of studies. Therefore, this study is purposed to observe the relationship between the thyroid functions and the lipid profiles in patients with struma and patients who seek treatment at the IDD clinic of research and development (R&D) center, Magelang. Information obtained from this will be very useful to know the relationship between the thyroid hormone and TSH with the lipid profile.

METHODS

This study was a non-interventional observational study with a cross-sectional design aimed to evaluate the relationship between thyroid functions and lipid profiles in patients with struma who came to the IDD clinic of R&D Center in Magelang during 2018. This location was chosen because many patients with struma sought treatment at the clinic. The study population in this study was women of childbearing age who had recently been treated at the IDD clinic. Its selected sample was women of childbearing age who came to the clinic and met inclusion and exclusion-criteria of this study. The inclusion criteria were new patients who have a struma, while exclusion criteria were those who had no any complications with metabolic diseases such as diabetes mellitus (DM). The sample selection was conducted by means of total sample, namely patients who came to the clinic in 2018 until the number of sample was fulfilled.

Data and sample characteristics were collected by questionnaire-based interview. Clinical data to determine health status and disease histories were collected by using a questionnaire by a physician from the Magelang research and development center. Participants suffering other complications were not included in this study. Data on physical indicators were collected by examining clinical signs by using a questionnaire. The nutritional status (height, body weight) was determined and collected anthropometrically by measuring height by using microtoise and weighing by using a Seca digital scale. Biochemical indicator data including TSH, free-T4 (fT4), LDL, HDL, and total cholesterol were obtained by taking blood from the veins as much as 3.5 ml according to procedures taken by the health analyst. The blood was rotated at high speed 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 -20^{o}C before analysis. The analysis of TSH, fT4, LDL, HDL, and total cholesterol used the ELISA method.

The relationships between total cholesterol, LDL, HDL, and triglyceride levels with TSH and fT4 were processed by using the Spearman correlation coefficient. Linear regression was used to determine the relationships between total cholesterol, HDL, LDL, and triglyceride levels with TSH and fT4 after calculating age. Then the total cholesterol, HDL, LDL, and triglyceride levels of patients with thyroids disorders were compared with euthyroid patients (patients with thyroid but normal thyroid function) by using a linear regression model, taking into account body mass index (BMI), age, and using hormonal contraception. Statistical analysis was conducted by using SPSS 22 with a significance of $p < 0.05$. This study was approved by the Universitas Islam Indonesia (UII) ethics committee.

RESULTS

This study was focused on women of childbearing age who were treated at the IDD clinic in Magelang. The samples selected were women of childbearing age who sought treatment at the clinic and met the inclusion-exclusion criteria as follows: new patients who had struma without histories of metabolic diseases such as DM. There were 83 patients who came for treatment in a period of January - July 2018 according to the sample calculation.

Description of the characteristics of the subjects/patients showed that average age of them was 33.5 ± 8.63 years and their level of education (74.3 %) was mostly more than 9 years (junior high school or college). Most of them was unemployment (50.6%). Anthropometric measurements showed the average body weight and height of them were 51.8 ± 9.28 kilograms and 152.3 ± 5.87 cm with normal BMI values of 22.3 ± 3.98. The nutritional status of them (61.4%) was included in a normal category. As many as 20.5% of them experienced overweight having risks of various chronic diseases, such as coronary heart disease (CHD), hypertension, and others. This situation should be followed up by enhancing a promotion of comprehensive and effective prevention efforts, such as promoting the general guidelines for balanced nutrition.

Table 1. Subject Charateristic Distributions

Variable	Number (83)
Age [mean ± standard deviation (SD)]	33.5 ± 8.63
< 20 years old	6 (7.2 %)
20 – 35 years old	39 (47.0 %)
> 35 years old	38 (45.8 %)
Education	
Elementary (not completed)	1 (1.2 %)
Elementary	20 (24.4 %)
Junior high school	21 (25.6 %)
Senior high school	27 (32.9 %)
College	13 (15.8 %)
Occupation	
Enterpreneur	6 (7.4 %)
Civil servant/military/police	4 (4.9 %)
Private sector	18 (22.2 %)
Labor/fishermen	4 (4.9 %)
Farmer	8 (9.9 %)
Unemployment	42 (50.6 %)
Nutritional state (BMI)	
Underweight (< 18.5)	15 (18.1 %)
Normal (18.5 – 24.9)	51 (61.4 %)
Overweight (≥ 25.0)	17 (20.5 %)

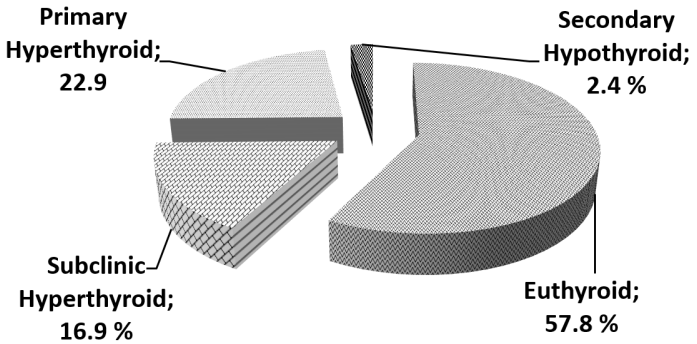

Figure 1. Distribution thyroid dysfunction cases of the subjects

Due to abnormal data distribution of the patients' TSH and fT4 levels, the data was presented as a median. Results of laboratory examination of thi study showed that the median values of the TSH and fT4 were still within normal limits. Thyroid function tests in a form of serum fT4 and TSH levels were standard tests to determine diagnosis of both hyperthyroid and hypothyroid cases. This indicator was used because the fT4 is a free active hormone that is not bound by thyroid binding-protein (TBG). Meanwhile, the T3 and T4 hormones are bound to TBG protein in plasma, thus it is strongly influenced by TBG levels.

The use of TSH to predict the thyroid hormone is related to its regulation by the T4 hormone in the pituitary level through a negative feedback mechanism.[10] Moreover, the TSH hormone was also used as a screening for congenital hypothyroidism in newborns and is the best indicator to detect primary hypothyroid symptoms in neonates.[3] Based on this, serum fT4 and TSH examination can be considered as an appropriate clinical diagnosis method to determine thyroid dysfunctions.[11]

The combination of TSH and fT4 levels to determine the clinical diagnosis of the patients showed that most of them (57.8%) only were suffering the struma, but the results of TSH and fT4 levels were normal (euthyroid). There was a shift in cases where there were more hyperthyroidism cases than hypothyroid cases (22.9% of them suffering hyperthyroidism and 16.9% suffering subclinical hyperthyroidism) (Figure 1).

Table 2. Biochemical Distribution of Subjects

Variable	Number (83)
TSH level (median (min-max))	0.52 (0.01 – 5.35)
Hyperthyroid (< 0.3 µIU/ml)	34 (41.0 %)
Normal (0.3 – 4.0 µIU/ml)	47 (56.6 %)
Hypothyroid (> 4.0 µIU/ml)	2 (2.4 %)
fT4 level (median (min-max))	1.31 (0.06 – 7.77)
Hypothyroid (< 0.8 ng/ dl)	6 (7.2 %)
Normal (0.8 – 2.0 ng/ dl)	60 (72.3 %)
Hyperthyroid (> 2.0 ng/ dl)	17 (20.5 %)
HDL level (mean ± SD)	53.0 ± 9.44
Normal (≥ 45 mg/dl)	68 (81.9 %)
Abnormal (< 45 mg/dl)	15 (18.1 %)
LDL level (mean ± SD)	106.6 ± 34.29
Normal (≤ 100 mg/dl)	33 (39.8 %)
Abnormal (> 100 mg/dl)	50 (60.2 %)
Total cholesterol level (mean ± SD)	171.7 ± 40.34
Normal (≤ 200 mg/dl)	65 (78.3 %)
Abnormal (> 200 mg/dl)	18 (21.7 %)

The results of the laboratory examination of the patients showed that the lipid profiles of them were within normal limits, except LDL levels that were slightly above the normal limit. Most patients (81.9%) had normal HDL levels and normal total cholesterol levels (78.3%), but most of them (60.2%) had LDL levels above normal.

The thyroid hormone could have a specific effect on the lipid metabolism to regulate cholesterol synthesis and degradation, and it also could mediate activities of key enzymes.[8] Changes in thyroid hormone levels would affect the biosynthesis of cell cholesterol, the cholesterol secretion by the liver, the process of converting HDL to VLDL in the liver, the activity of Lipoprotein Lipase (LPL) enzymes in cell membranes, and the modulation of the body's LDL receptor activity. Thus, changes in the process of lipid metabolism could result changes in blood lipid profiles.[5,8]

Table 3. Relationship between Thyroid Function and Lipid Profiles

	TSH	fT4
Total Cholesterol	0.518	-0.517
	p=0.000	p=0.000
HDL	0.028	-0.257
	p=0.814	p=0.019
LDL	0.538	-0.536
	p=0.000	p=0.000

Table 4. Thyroid function and lipid profile according to diagnosis

	Subclinic hyperthyroid (14)	Euthyroid (48)	Hyperthyroid (19)
Age, mean±SD	35.6 ± 9.34[d]	34.1 ± 8.64	31.0 ± 7.97[a]
BMI, mean±SD	22.3 ± 4,13[d]	23.4 ± 4.13	20.2 ± 2.46[b]
fT4, (median, min-max), ng/L	1.2(0.69-1.77)[e]	1.2(0.66-1.66)	6.8(0.97-7.77)[c]
TSH, (median, min-max), µIU/ml	0.05(0.01-4.36)[f]	1.4 (0.05-5.35)	0.03(0.01-0.08)[c]
Total Cholesterol, mean±SD, mg/dl	181.6 ± 32.07[d]	187.3 ± 33.66	122.8 ± 20.09[b]
P (unadjusted)*	0.577	-	0.000
P (adjusted with age, BMI)*	0.719	-	0.000
HDL, mean±SD, mg/dl	57.4 ± 11.04[d]	53.6 ± 8.49	48.8 ± 9.66[b]
P (unadjusted)*	0.185	-	0.049
P (adjusted with age, BMI)*	0.229	-	0.026
LDL, mean±SD, mg/dl	110.5 ± 14.83[d]	121.7 ± 29.71	63.5 ± 16.33[b]
P (unadjusted)*	0.181	-	0.000
P (adjusted with age, BMI)*	0.250	-	0.000

a. independent t test indicated that there was no significant difference between euthyroid and hyperthyroidism.
b. independent t test indicated that there is a significant difference between euthyroid and hyperthyroidism.
c. different Mann-Whitney test indicated that there was a significant difference between euthyroid and hyperthyroidism.
d. independent t test indicated that there was no significant difference between euthyroid and subclinical hyperthyroidism.
e. different Mann-Whitney test indicated that there was no significant difference between euthyroid and subclinical hyperthyroidism.
f. different Mann-Whitney test indicated that there was a significant difference between euthyroid and subclinical hyperthyroidism.
* linear regression with significance <0.05

There was a significant positive relationship between the TSH levels, the total cholesterol and the LDL, but there was no significant relationship between the TSH levels and the HDL (Table 3). This showed that the higher the TSH level, the higher the total cholesterol and LDL level. Likewise, the fT4 levels were inversely related to the total cholesterol and LDL cholesterol, but there was no relationship between the fT4 and HDL. This could mean if the fT4 levels increase, a total cholesterol and LDL would decrease. Both findings proved to be statistically significant.

After calculating age, the relationship between the TSH, the total cholesterol and the LDL remained significant (both p = 0.000), whereas there was no significant relationship between the HDL and the total cholesterol (p <0.000). Meanwhile, the HDL (p = 0.016) and the LDL (p = 0.000) still showed a significant relationship to the fT4 after calculating age. Table 4 presents the clinical diagnosis, thyroid function, and lipid profile of the patients. Patients with secondary hypothyroidism were not included in the table because there were only 2 patients, therefore the data did not meet the requirements. The age of them based on diagnosis group ranged from 31 - 35 years and was spread evenly, so there were no significant differences between the groups. The nutritional status of them according to the diagnosis group was in the normal category (between 19.5 - 25.0) as there was a significant difference of the BMI between the hyperthyroid and euthyroid groups. There were no significant differences between the subclinical hyperthyroid groups and euthyroid groups. Hyperthyroidism could cause the body's metabolism to increase, and one of the symptoms that appear could be weight lose. Compared to other diagnosis groups, the hyperthyroid groups had the lowest BMI.

Total blood cholesterol levels in hyperthyroid group were lower and significantly different when compared with euthyroid group (122.8 ± 20.09 mg/dl vs 187.3 ± 33.66 mg/dl). It was also seen in subclinical hyperthyroidism group, even though this group was not statistically significant. HDL levels in hyperthyroid group were lower and significantly different when compared with euthyroid group (48.8 ± 9.66 mg/dl vs 53.6 ± 8.49 mg/dl) but they were higher in subclinical hyperthyroid group although not statistically significant. LDL levels in hyperthyroid group were lower and significantly different when compared with euthyroid group (63.5 ± 16.33 mg/dl vs 121.7 ± 29.71 mg/dl). Similarly, the subclinical hyperthyroid group also had a lower LDL level although not statistically significant.

DISCUSSION

Struma or goiter is a condition due to an increase of a thyroid gland, therefore the gland is more active in producing thyroid hormones. Globally, there has been an increase of struma cases since 30 years ago probably due to increased diagnostic activities and increasing abilities to detect the struma with excellent diagnostic technologies.[12,13] Most studies report an increase of the cases may be caused by iodine deficiency, although its causes have not been fully understood until now.[12]

In this study, many patients who came to the clinic with enlarged thyroid nodules suffer from hyperthyroidism although the majority of cases (57.8%) were euthyroidism. Severe and prolonged iodine deficiency could increase risks of struma and hypothyroidism. However, an increase of iodine intakes in the populations of the endemic areas of IDD would increase incidences of hyperthyroidism, especially in severe endemic areas.[14] Aged patients with enlarged thyroid nodules were at greater risks of developing hyperthyroidism, even though at the beginning of iodine fortification they have normal thyroid hormone levels. This occurs because older adults have irrepressible radioactive iodine uptakes and low TSH levels that do not respond to the T4 hormone; therefore, the TSH and T4 are not corrected.[14] Although thyroid nodules with hyperthyroidism tend to occur in older individuals, the clinical manifestations from hyperthyroidism may not be related to it at all; many of them exhibit symptoms related to heart disease, often atrial fibrillation.[15]

Increasing iodine intake can also induce autoimmune hyperthyroidism disease (Grave's disease). Several studies have shown that autoimmune hyperthyroidism is higher in populations in endemic areas of IDD. This is because individuals, who have struma and are found in many endemic areas of IDD, often have antibodies on their systemic circulations. It is estimated that increasing iodine intakes will increase thyroglobulin productions and results in thyroid autoimmunity.[14] The hyperthyroidism due to autoimmunity may affect all ages with clinical manifestations of heat intolerance, tachycardia, tremor, weight

loss, and orbitopathy.[15]

The diagnosis of hyperthyroidism, hypothyroidism, and euthyroid was based on a combination of TSH and fT4 levels. Normal TSH levels are around 0.4-4.0 μU/l, whereas normal reference intervals for fT4 levels range from 0.7 to 2.1 ng/dl, due to negative feedback systems involving the hypothalamus, pituitary, and thyroid glands.[16] In certain cases, TSH and fT4 are not adjusted according to a negative feedback mechanism due to other thyroid diseases, for example, thyroid cancer, etc.[10] This proves that the regularity of TSH and fT4 levels are still within normal limits and does not lead to diseases other than above.

On the lipid metabolism, TSH can have an independent effect such as inducing adipogenesis and lipolysis,and it can increase HMG_CoA activity.[17,18] The later is an enzyme that inhibits rates of cholesterol synthesis and increases cholesterol content in the liver.[6] In this study, TSH could be positively related to total cholesterol and LDL cholesterol, meaning an increase of the TSH would increase total cholesterol and LDL levels. Similarly, results of other studies show that there is a relationship between the increase of TSH eventhough in a normal range and the increase of lipid profile (increased cholesterol, LDL, and triglycerides) which is less favorable.[20-23]

The levels of total blood cholesterol, LDL, and HDL in hyperthyroid patients in this study were lower and significantly different when compared to euthyroid patients. This is consistent with results of Zhenjiang's study that cholesterol and LDL levels in both the hyperthyroid and subclinical hyperthyroid groups were significantly lower than controls, whereas HDL levels were only significantly lower in the hyperthyroid group.[24] Chen et al. reported that hyperthyroid patients had significantly lower HDL and LDL levels compared to euthyroid patients, but not at cholesterol levels.[25] Selim et al. reported that hyperthyroid patients had lower total cholesterol and LDL levels, free-T3 (fT3) and fT4 that were inversely correlated with cholesterol, LDL, and HDL levels, whereas TSH correlates with cholesterol, LDL, and HDL.[26]

Thyroid hormones are very important to maintain adequate cholesterol to meet the body's need and function to regulate important steps of cholesterol synthesis, absorption, and metabolism.

Thyroid hormones regulate cholesterol levels by stimulating liver synthesis, serum uptake, and intrahepatic conversion to bile acids.[27] The literature shows various reports of changes in lipid profiles in hyperthyroid patients. The decrease of cholesterol, LDL, and HDL levels in hyperthyroid patients may be caused by several factors. Thyroid hormones are able to regulate expressions of LDL receptors that cause changes in cellular uptake and LDL catabolism.[25] Thyroid hormones increase the expression of the binding protein binding factor sterol-2 (SREBP-2) which modulates LDL-R expression.[6] This process will increase the activity of LDL cell receptors and LDL uptake from circulation to the tissue will increase so that LDL levels in circulation decrease.[5,8]

Thyroid hormone induces the HMG-CoA reductase activity and the expression of the farnesyl pyrophosphate gene to increase cholesterol synthesis, so it rises the biosynthesis of endogenous cholesterol in the liver.[10] This hormone causes lipoprotein lipase activity to accelerate the use of cholesterol in peripheral tissues and increases the level of cholesterol clearance which results a decrease of blood cholesterol levels.[25] Moreover, it also increases the use of cholesterol in peripheral tissues and accelerates excretion bile acids and bile there by reducing total cholesterol levels in the blood.[24] Modulation of HDL metabolism is achieved by increasing the activity of CETP cholesteryl ester transfer protein which converts high-density lipoprotein (HDL) to very-low-density lipoprotein (VLDL). This causes the rate of conversion of HDL to VLDL increases so that the excretion of cholesterol in the liver increases. Because of the rapid increase in conversion from HDL to VLDL, it causes a decrease in circulating HDL levels.[5,8] Adequate levels of HDL can prevent cholesterol from settling in the arteries

(atherogenesis) and protect blood vessels from the process of atherosclerosis. Low levels of HDL in the blood can have a detrimental effect on the body that can lead to coronary heart disease (CHD).[10] Increased risk of heart disease can be influenced by HDL function and changes in lipid profile levels.[22] HDL plays an important role in modifying formation and development of plaque (anti-atherosclerosis). These particles also have anti-inflammatory properties, so inflammation that encourages lipid deposition will be inhibited. Besides, HDL can also remove some oxidized (anti-oxidative) lipids.[10]

The state of hyperthyroidism is characterized by an increase in oxidative metabolism and a decrease in plasma lipids and plasma lipoproteins. The hypermetabolic state accelerates the production of free radicals in the mitochondria and induces changes in the antioxidant defense system. High oxidative stress status can modify oxidative LDL and play an important role in atherosclerosis and risk of coronary heart diseases. In hyperthyroid patients, increased LDL oxidation is closely associated with high levels of free thyroxine (fT4). Meanwhile, in LDL oxidation, hypothyroidism is strongly influenced by cholesterol and LDL levels.[28] This causes hyperthyroid patients to have higher risks of suffering coronary heart diseases.

In addition, a decrease in cholesterol levels below normal values can have a harmful effects on the body. Cholesterol has a central role in the production of liver bile and a major component of cell membrane formations and intracellular structures. Cholesterol also functions as a precursor in the biosynthesis of several vitamins, steroids, and sex hormones. Early epidemiological studies show relationships between low cholesterol levels and risks of cancer, intracranial hemorrhage, and death.[29] A decrease in cholesterol levels causes disruption of the physiological processes of brain neurons so that a decrease in serotonin levels as a neurotransmitter regulates mood centers in the brain and results disruption mental health.[5,8] Conversely, cholesterol levels will increase in hypothyroid patients. The hypothyroid state will cause a decrease in lipoprotein receptors so that lipoprotein catabolism decreases and results hypercholesterolemia, an increase in total cholesterol, and LDL cholesterol.[6]

CONCLUSION

The combination of TSH and fT4 levels to determine the clinical diagnosis in the patients with struma showed that more than half of them only had enlarged thyroid nodules with normal TSH and fT4 (euthyroid) levels, and one-fifth of them had hyperthyroidism. There was a significant positive relationship between the TSH levels and the total cholesterol as well as the LDL after calculating age. However, there was no significant relationship between the TSH levels and the HDL. There was a significant negative relationship between the fT4 levels, the total cholesterol and the LDL cholesterol, but there was no relationship between the fT4 and the HDL. After calculating age, the HDL showed a significant relationship with the fT4. The total blood cholesterol, HDL and LDL cholesterol levels in hyperthyroid patients were lower and significantly different when compared to euthyroid patients, but they were not significant in subclinical hyperthyroid patients.

CONFLICT OF INTEREST

This study does not have a conflict of interest with any party.

ACKNOWLEDGEMENT

The authors thank to the Universitas Islam Indonesia Yogyakarta for funding this study. The authors also thank to the Head of the Magelang research and development center for giving permission to take the data at the Clinic. In addition, the authors thank to the patients and the research team involved in this study.

REFERENCES

1. Aburto NJ, Abudou M, Candeias V, Tiaxiang Wu P. Effect and safety of salt iodization to prevent iodine deficiency disorders: A systematic review with meta-analyses WHO Library Cataloguing-in-Publication Data.

2014;91–3.
2. Vanderpump MPJ. Epidemiology of thyroid disorders. In: Luster M, Duntas LH, Wartofsky L, editors. The thyroid and its diseases a comprehensive guide for the clinician. Switzerland: Springer; 2019. p. 75–86.
3. WHO. Assessment of the iodine deficiency disorders and monitoring their elimination. WHO, Geneva. 2007;1–107.
4. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol. 2015;3(4):286–95.
5. Rizos C, Elisaf M, Liberopoulos E. Effects of thyroid dysfunction on lipid profile. The Open Cardiovascular Medicine Journal. 2011;5:76–84.
6. Delitala AP, Fanciulli G, Maioli M, Delitala G. Subclinical hypothyroidism, lipid metabolism and cardiovascular disease. Eur J Intern Med. 2017;38:17–24.
7. Peppa M, Betsi G, Dimitriadis G. Lipid Abnormalities and Cardiometabolic Risk in Patients with Overt and Subclinical Thyroid Disease. Journal of Lipids. 2011;2011(Vldl):1–9.
8. Duntas LH, Brenta G. The Effect of Thyroid Disorders on Lipid Levels and Metabolism. Medical Clinics of North America. 2012;96(2):269–81.
9. Liu J, Liu L, Jia Q, Zhang X, Jin X, Shen H. Effects of excessive iodine intake on blood glucose, blood pressure, and blood lipids in adults. Biological Trace Element Research. 2019;192(2):136–44.
10. Gropper SS, Smith JL, Carr TP. Advanced nutrition and human metabolism. Seventh. Boston: Cengage Learning; 2018. 528–533 p.
11. Djokomoeljanto R. Kelenjar Tiroid-Hipotiroid-Hipertiroid. In: Buku Ajar Ilmu Penyakit Dalam Jilid III. ke-5. Jakarta: Interna Publishing; 2009. p. 1993–2008.
12. Zheng X, Long J, Ren W, Liu C, Wei Q, Luo R, et al. Exposure to the Chinese famine in early life and the thyroid function and nodules in Adulthood. Endocrine Practice. 2019;25(6):598–604.
13. Park VY, Han K, Seong YK, Park MH, Kim EK, Moon HJ, et al. Diagnosis of thyroid nodules: Performance of a deep learning convolutional neural network model vs. radiologists. Scientific Reports. 2019;9(1):1–9.
14. Zimmermann MB. The Thyroid and Its Diseases. Luster M, Duntas LH, Wartofsky L, editors. The Thyroid and Its Diseases. A Comprehensive Guide for the Clinician. Cham: Springer International Publishing; 2019. 101–108 p.
15. LiVolsi VA, Baloch ZW. The pathology of hyperthyroidism. Front Endocrinol (Lausanne). 2018 Dec 3;9:1–8.
16. Stockigt J. Clinical strategies in the testing of thyroid function. In: Endotext. MDText.com Inc; 2011. Available from: www.endotext.org
17. Lu S, Guan Q, Liu Y, Wang H, Xu W, Li X, et al. Role of extrathyroidal TSHR expression in adipocyte differentiation and its association with obesity. Lipids Health Dis. 2012;11:1–12.
18. Gagnon AM, Antunes TT, Ly T, Pongsuwan P, Gavin C, Lochnan HA, et al. Thyroid-stimulating hormone stimulates lipolysis in adipocytes in culture and raises serum free fatty acid levels in vivo. Metabolism. 2010;59(4):547–53.
19. Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, et al. A novel role for thyroid-stimulating hormone: Up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protei. Hepatology. 2010;52(4):1401–9.
20. Waterhouse DF, McLaughlin AM, Walsh CD, Sheehan F, O'Shea D. An examination of the relationship between normal range thyrotropin and cardiovascular risk parameters: A study in healthy women. Thyroid. 2007;17(3):243–8.
21. Xu C, Yang X, Liu W, Yuan H, Yu C, Gao L, et al. Thyroid stimulating hormone, independent of thyroid hormone, can elevate the serum total cholesterol level in patients with coronary heart disease: A cross-sectional design. Nutrition & Metabolism. 2012;9:1–8.

22. Jung KY, Ahn HY, Han SK, Park YJ, Cho BY, Moon MK. Association between thyroid function and lipid profiles, apolipoproteins, and high-density lipoprotein function. Journal of Clinical Lipidology. 2017;11(6):1347–53.
23. Wang F, Tan Y, Wang C, Zhang X, Zhao Y, Song X, et al. Thyroid-stimulating hormone levels within the reference range are associated with serum lipid profiles independent of thyroid hormones. The Journal of Clinical Endocrinology and Metabolism. 2012;97(8):2724–31.
24. Zhenjiang H. The correlation of blood lipid profile and its ratio, cystatin C and homocysteine of thyroid dysfunction. American Journal of Clinical and Experimental Medicine. 2017;5(4):108.
25. Chen Y, Wu X, Wu R, Sun X, Yang B, Wang Y, et al. Changes in profile of lipids and adipokines in patients with newly diagnosed hypothyroidism and hyperthyroidism. Scientific Reports. 2016;6:1–7.
26. Selim FO, Ahmed AM. The Association between serum paraoxonase-1 activity, thyroid hormones and lipid profile in patients with primary hyperthyroidism. International Journal of Advanced Research. 2014;2(11):172–81.
27. Sinha RA, Singh BK, Yen PM. Thyroid hormone regulation of hepatic lipid and carbohydrate metabolism. Trends in Endocrinology & Metabolism. 2014;25(10):538–45.
28. Costantini F, Pierdomenico SD, De Cesare D, De Remigis P, Bucciarelli T, Bittolo-Bon G, et al. Effect of thyroid function on LDL oxidation. Arteriosclerosis, Thrombosis, and Vascular Biology. 1998;18(5):732–7.
29. Giugliano RP, Wiviott SD, Blazing MA, De Ferrari GM, Park JG, Murphy SA, et al. Long-term safety and efficacy of achieving very low levels of low-density lipoprotein cholesterol: A prespecified analysis of the IMPROVE-IT trial. JAMA Cardiology 2017;2(5):547–55.