ORIGINAL ARTICLE

Correlation between Fasting Lipid, Total Body Fat, Body Mass Index and Thyroid Status among Patients with Thyroid Disorders.

Ishak FM[a,d] , Wan Mohamed WMI[b,d] ,Tuan Ismail TS[c,d], Haron J[a,d]

[a] *Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia.*
[b] *Department of Internal Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia.*
[c] *Department of Chemical Pathology, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia.*
[d] *Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia.*

ABSTRACT

INTRODUCTION: Thyroid dysfunction affects lipid metabolism via lipoprotein transport. In this study, we compared the fasting lipid profile, body mass index and percentage of total body fat among patients with different thyroid status and its correlation with thyroid function test. **MATERIALS AND METHODS**: We conducted a cross sectional study over 28 months among patients with different thyroid status from Oncology Clinic and Endocrine Clinic at Hospital Universiti Sains Malaysia. Adult patients aged 18 years to 80 years, hyperthyroid or hypothyroid of at least 6 months or euthyroid of least 1 year were eligible. The total percentage of body fat was measured using DEXA scan. The thyroid function test and fasting lipid profiles were documented. **RESULTS:** There was no significant mean difference of triglyceride (TG), total cholesterol (T-Chol), LDL, HDL, BMI and percentage of total body fat among patients with different thyroid status ($p>0.050$). Among hypothyroid patients, T-Chol and HDL were positively correlated with TSH ($r=0.43$, $r=0.36$). The free T4 was inversely correlated with the percentage of total body fat among patients with euthyroid status ($r=-0.50$). The TSH was negatively correlated with the percentage of total body fat among patients with hyperthyroid status ($r=-0.28$). **CONCLUSION**: A positive correlation between TSH with T-Chol and negative correlation between free T4 with T-Chol among hypothyroidism status suggests a potential reduction of risk for cardiovascular events among this group.

Keywords
Fasting Lipid Profile, Thyroid Disorder, BMI, Percentage of Total Body Fat

Corresponding Author
Dr. Juhara Haron.
Department of Radiology, School of Medical Sciences, Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia.
No phone: +60129081990
Email: drjuhara@usm.my

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INTRODUCTION

Dyslipidaemia is one of the established risk factors for cardiovascular disease. Our study aimed to look for correlation between lipid profile, body mass index and percentage of total body fat among patients with thyroid disorder with different thyroid statuses (hyperthyroid, hypothyroid and euthyroid).

Thyroid disorders are amongst one of the most common and prevalent endocrine and metabolic diseases in Malaysia. The risk of atherosclerosis among patients with thyroid dysfunction is supported by the association between thyroid status and lipid metabolism with dyslipidaemia playing a major role.[1,2] The lower level of total cholesterol (T-Chol) and LDL were shown in patients with hyperthyroidism in multiple studies.[3,4] Lower levels of triglycerides (TG), HDL, apoA1, apoB and Lp (a) levels had been found in patients with hyperthyroidism compared with euthyroid controls in other studies.[5-7] Qualitative lipid changes including increased levels of oxidized LDL, higher contents of thiobarbituric acid reactive substances and dienes in LDL, low paraoxonase activity in HDL particles, and lower LDL contents in antioxidant vitamin E and β-carotene were found in patients with hyperthyroidism.[8] One study found normal levels of LDL, HDL, TG, Lp (a), apoA1 and apoB among hyperthyroid patients while another study found lower level of total cholesterol and LDL.[9]

High levels of T-Chol and LDL are some of the common findings in patients with clinical hypothyroidism.[5] An increased level of markers of lipid peroxidation, such as malondialdehyde (MDA) and acid reactive substances as a consequence of enhanced LDL oxidation had been reported in clinical hypothyroidism.[10] According to Tzotzas T. and Teixeira *et al*, the changes in the thyroid hormone levels in hypothyroidism were associated with total and LDL cholesterol levels abnormalities. They found that the level of TG, apoB, apoA1, Lp (a) levels and qualitative abnormalities might be still normalized or remained unchanged, due to more complex cause of dyslipidaemia in hypothyroidism.[11]

There are an increase in high sensitivity C-reactive protein and coagulation deficit levels in patients with hypothyroidism.[12] The underlying causes are the decrease in glycogen synthesis, glucose oxidation, impaired intracellular glucose catabolism, GLUT4 translocation and alteration in blood flow.[13] Some studies on patients with overt and subclinical hypothyroidism reported an increase in intima-media thickness of the common carotid artery.[14] An increased occurrence of ischemic stroke and higher frequency and/or severity of coronary heart disease have been reported in patients with overt hypothyroidism.[2] Subclinical hypothyroidism was reported to have an association with diastolic hypertension.[15] According to Whickham Survey, the incidence of coronary heart disease and related mortality in subclinical hypothyroid patients over 20 years of follow up was attenuated after levothyroxine treatment.[16] In addition, subclinical hypothyroidism was associated with a significant risk of coronary artery disease and cardiovascular mortality, as suggested by 3 meta analyses.[17] Besides that, another study found subclinical hypothyroidism association with cerebral ischaemia.[18]

We included all patients with thyroid disease; with treatment (e.g. on medication or ablation) or without treatment. Some examples of thyroid diseases were multinodular goitre, autoimmune disease (Graves'/ Hashimoto's disease), thyroid cancer etc.

Body composition composes of lean mass, fat mass and body mineral content. Thyroid dysfunction affects body composition but the effect of alteration in thyroid status among patients with thyroid disorder on total body fat remains unclear. In this study, our focus is on the percentage of total body fat which is the sum of fat in the trunk, leg, arm and visceral fat. One of the studies proved that after the initial treatment of hyperthyroidism, only lean mass (fat free mass) was recovered, but later at 12 months, an increase in fat mass was found.[19] Higher levels of body mass index (BMI) and adiposity caused an elevation in serum free T3 levels but did not influence free T4 levels.[20] This demonstrated that the elevated free T3 generated from higher fat mass has a negative effect on fat mass.[21] It was postulated that an increase in fat mass resulted in an increased generation of free T3 from free T4. Subsequently, an increased free T3 production in fat lead to an increase in free T3. It was important to note that an increase in deiodinase 2 conversion of free T4 to free T3 in fat was required. This enzyme was expressed in brown but not substantially expressed in white adipose tissues.[22]

The results of the study could be used as management guidelines and exploring the benefit of lipid profile screening in patients with thyroid disorders.

MATERIALS AND METHODS

Patients

We conducted a cross-sectional single-centered study in patients who attended the Oncology Clinic and Endocrine Clinic at Hospital Universiti Sains Malaysia (HUSM) over a period of 27 months from June 2016 until September 2019. Adult patients age d 18 years to 80 years with thyroid disease were randomly selected. Hyperthyroid status was defined as biochemically hyperthyroid with or without anti -thyroid medication for the last 6 months (TSH <0.270 mIU/L and free T4 >22 pmol/L or normal). Hypothyroid status was taken as biochemically hypothyroid with or without medication for the last 6 months (TSH >4.2 mIU/L and free T4 <12 pmol/L or normal). Euthyroid status was taken as patient who previously had hyperthyroid or hypothyroid and became biochemically euthyroid for a minimum period of 1 year with or without medication (TSH 0.270 to 4.20 mIU/L and free T4 12 to 22 pmol/L). Pregnant and lactating women, history of

steroid ingestion (2 weeks prior to blood taking and dual energy X-ray absorptiometry), patient on anti-lipid medication, body weight of more than 150 kg, underlying chronic gastrointestinal upset (loose stool or diarrhea of more than 3 months) and patients with history of gastric and small bowel resection were excluded.

The number of patients required for each different thyroid status group was determined using a single mean formula. We recruited a sample of 220 patients with

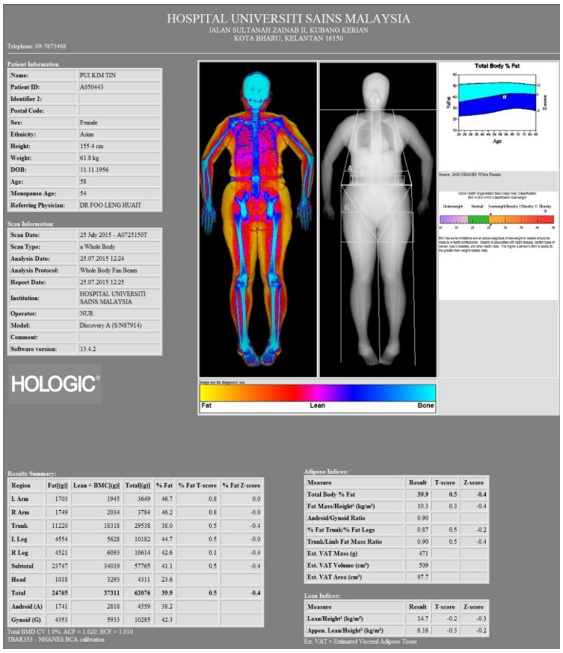

Figure 1: Dexa scan images with detailed value of lean body mass, fat mass (percentage of total body fat) as well as body mineral content. The yellow arrow in the figure shows percentage of total body fat.

thyroid disorders by non-randomized, purposive sampling. Detailed information of the patients and written informed consent was obtained from each patient. After exclusion and incomplete data obtained, the final number of patients included was 159.

Data Collection

The percentage of total body fat was measured using dual energy X-ray absorptiometry (DEXA) scanning on Hologic QDR 4500W scanner. It was taken as a sum of the percentage of fat in the trunk, leg, arm and visceral fat. The DEXA was performed according to the standard protocol for bone densitometry measurement. The subjects were made to lie in a supine position on the DEXA gantry and scanning was performed using very low (0.001mSv) radiation exposure. Based on the X-ray attenuation properties, the lean mass, bone mineral content and fat mass were generated automatically (Figure 1).

The body weight was measured on SECA scale 220 model, which has a maximum weight of 300 kg and a precision of 200 g with the patient barefooted and in light clothing. The height was measured using a metal stadiometer which measurement range of 60 to 200 cm , with a precision of 1 mm with the patient in standing position, leg in a full stretch with the feet in parallel. The BMI was calculated using the formula of BMI = weight (kg) / height^2 (m).

A total of 2 ml of fasting venous blood for TG, T-Chol, HDL and LDL were taken and analyzed using Architect C8000 analyzer. The level of thyroid stimulating hormone (TSH) and free T4 were taken from the laboratory information system.

Statistical Analysis

The data collected was analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, SPSS Inc.© (version 24, SPSS Inc., Chicago, IL, USA). The level of TSH, free T4, percentage of total body fat, TG, T-Chol, LDL, HDL and BMI were expressed as mean ± standard deviation (SD).

One-way ANOVA test was used to compare the mean of TG, T-Chol, HDL, LDL, percentage of total body fat and BMI among patients with different thyroid statuses. Pearson correlation analysis was used to determine the correlation between TG, T-Chol, HDL, LDL, percentage of total body fat, BMI and thyroid function test (TSH, free T4) of patients with different thyroid status. P-value of less than 0.05 ($p<0.05$) was considered statistically significant.

This study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM code: USM/JEPeM/17060298), which complies with the Declaration of Helsinki.

RESULTS

Table 1: Profile of patients (n=159)

	Mean (SD)	n (%)
Age (years)	38.20 (13.50)	
Gender		
Male		50 (31.4)
Female		109 (68.6)
Race		
Malay		148 (93.1)
Chinese		11 (6.9)
Status		
Hyperthyroid		68 (42.8)
Hypothyroid		37 (23.3)
Fasting Lipid (mmol/L)		
TG	1.41 (0.91)	
T-Chol	5.16 (1.38)	
HDL	1.26 (0.33)	
Thyroid function test		
Percentage of Total body Fat (%)	35.61 (7.24)	
BMI (kg/m^2)	25.61 (5.03)	

A total of 159 participants were recruited for this study; 68 were hyperthyroid, 37 were hypothyroid and 54 were euthyroid. The mean age of the participants was 38.20 years (±13.50). Malay and female participants were predominant in the study with n=148 (93.1%) and n=109 (68.6%) respectively. The mean percentage of total body fat was 35.61 (±7.24) and BMI was 25.61 (±5.03) (kg/m^2).

One-way ANOVA shown no significant difference between the mean value of TG, T-Chol, LDL, HDL, BMI and percentage of total body fat among hyperthyroid, hypothyroid and euthyroid group (p >0.05). The TG, T-Chol, percentage of total body fat and BMI were noted to be higher and HDL was lower in hypothyroid as compared to euthyroid status. The result is summarized and shown in Table 2.

The total body fat was noted to be lower in the euthyroid group and higher BMI was noted in the hyperthyroid group. There was a significant difference found between the mean value of TSH and free T4 among hyperthyroid, hypothyroid and euthyroid patients. There was no significant correlation noted between TSH or free T4 with TG, T-Chol, HDL, LDL and BMI except for TSH and percentage of total body fat (r = -0.28, p=0.021) among patients with hyperthyroid status.

There was a significant positive correlation noted between TSH and T-Chol (r=0.43, p=0.008) and between TSH and HDL (r=0.36, p=0.027) whereas there was a significant inverse correlation noted between free T4 and T-Chol (r=-0.42, p=0.010) and between free T4 and HDL (r=-0.39, p=0.016) among patients with hypothyroid status.

The free T4 was inversely correlated with percentage of total body fat (r=-0.50, p <0.001) and BMI (r=-0.47, p<0.001) but not with TG, T-Chol, HDL or LDL, but there was no significant correlation noted between TSH

Table II: Comparison of mean TG, T-Chol, HDL, LDL, percentage of total body fat and BMI among different thyroid statuses (n=159)

Variables	Mean (SD)			F-statistic	p value
	Hyperthyroid (n=68)	Hypothyroid (n=37)	Euthyroid (n=54)		
TG (mmol/L)	1.48 (0.91)	1.58 (1.20)	1.20 (0.61)	2.39	0.095
T-Chol (mmol/L)	4.99 (1.36)	5.37 (1.83)	5.24 (0.99)	1.04	0.365
HDL (mmol/L)	3.28 (1.06)	3.31 (1.16)	3.39 (0.90)	0.17	0.842
LDL (mmol/L)	1.20 (0.29)	1.30 (0.39)	1.30 (0.32)	1.66	0.193
Percentage of total body fat (%)	36.78 (7.01)	35.22 (6.73)	34.26 (7.72)	1.90	0.154
BMI (kg/m^2)	26.18 (4.29)	25.74 (6.01)	24.77 (5.15)	1.19	0.031
TSH (mIU/L)	0.53 (1.53)	52.36 (37.65)	1.70 (1.05)	113.79	<0.001*
T4 (pmol/L)	30.41 (15.41)	9.32 (6.90)	16.75 (15.41)	51.72	<0.001*

Table III: Pearson Correlation of TG, T-Chol, HDL, LDL, percentage of total body fat and BMI with TSH and free T4 among different thyroid statuses express in (r = strength of correlation).

*Correlation is significant at the 0.05 level (1-tailed)

Thyroid status	TFT	TG	T-Chol	HDL	LDL	Percentage of total body fat	BMI
Hyperthyroid	TSH	-0.07	-0.06	-0.08	-0.08	-0.28*	-0.02
	T4	0.14	-0.19	0.23	-0.02	0.17	-0.13
Hypothyroid	TSH	0.06	0.43*	0.36*	0.31	-0.05	-0.28
	T4	-.024	-0.42*	-0.39*	-0.30	-0.10	0.26
Euthyroid	TSH	0.17	-0.20	-0.26	-0.19	0.11	
	T4	0.03	0.06	0.15	0.02	0.50*	-0.47*

and all lipid profiles, BMI and percentage of body fat among patients with euthyroid status.

DISCUSSION

Profile of patients

Thyroid hormones affect the key metabolic pathway which control energy balance by regulating energy storage and expenditure.[23] The mean age of participants in our study was 38.20 years old suggests a higher prevalence of thyroid dysfunction in the younger age and middle age group could be attributed to stress and environmental pollutants.[24] The majority were female (n=109, 68.6%), corresponded with the results published by other studies.[25-27] Greater risk of developing thyroid status disorder among females due to sex difference in the prevalence of autoimmune diseases.[28]

Comparison of mean TG, T-Chol, HDL, LDL, percentage of total body fat and BMI among different thyroid statuses.

There was no significant difference between TG, T-Chol, HDL, percentage of total body fat and BMI as the sample size of the thyroid population was small. Hypothyroid patients were treated promptly as mostly the causes of the disease were curable. Therefore, a large number of participants was not possible. Sangeeta *et al.* found that the TG, T-Chol and HDL were significantly lower while LDL was found to be higher in overt hyperthyroidism patients than controls. On the other hand, there was a decrease in HDL and TG while an increase in T-Chol and LDL in subclinical hyperthyroidism.[3] The decrease in HDL reported in hyperthyroidism could be due to an increase in CETP-mediated transfer cholesteryl esters from HDL to VLDL and an increase in HL-mediated catabolism of HDL2 while TG levels remained unchanged.[29]

An intervention study on free T4 administration to mild hypothyroidism patients showed no changes in BMI[30] while the other study higher BMI was found among women with subclinical hypothyroidism.[31] It was postulated that the association between TSH and body weight observed was caused by signals from adipose tissue which influenced the central regulation of thyroid function through stimulation of TRH by down-regulating the thyroid function in the states of energy deficits.[7, 32]

Our study shown that the percentage of total body fat between different thyroid status corresponded with previous studies. A short term (14 days) experiment on hyperthyroidism showed a decrease in fat free mass without a simultaneous reduction in total body fat. The study showed that there was no increment in body fat after 3 months but the increase was seen after 12 months of treatment.[19] Sánchez A. *et al.* found similar results after normalization of thyroid levels with oral L-Thyroxine. Their patients lost a modest amount of weight, averaging 3 kg but the fat mass did not change significantly.[33]

According to Diana Boj Carceller *et al.*, there was no difference in body composition between groups (control vs hyperthyroidism groups), although there was a trend for the treatment group to have more fat mass as they believed hyperthyroidism accelerated protein catabolism and the oxidation of amino acids resulting in a net loss of protein. Lipid accumulation during recovery of

hyperthyroidism appeared to be related to the decrease in lipolysis.[26]

There was no previous study to compare TSH and free T4 results among different thyroid status groups.

Correlation between TG, T-Chol, HDL, LDL, percentage of total body fat and BMI among different thyroid statuses.

Hyperthyroid status

We found a significant negative correlation between TSH and the percentage of total body fat. A study found decreased levels of TG and T-Chol in overt hyperthyroidism. However, in subclinical hyperthyroidism, there was an increase in T-Chol level but statistically not significant. Despite the increased activity of HMG-CoA reductase, T-Chol and LDL levels tend to increase in subclinical hyperthyroidism due to augmented excretion of cholesterol by bile together with enhanced receptor mediated catabolism of LDL particles.[34] Variations observed in TG levels could be due to the action of thyroid hormone on VLDL. In hyperthyroidism, an acceleration of catabolism of VLDL was due to changes in the activity of lipoprotein lipase and or hepatic TG lipase.[3, 4] To date, no study was done regarding the correlation between TSH/free T4 and BMI among hyperthyroidism subjects. A Belgian study demonstrated there were no correlations between TSH and the whole body fat mass, and a South Korean study in men found no association between TSH and visceral and subcutaneous fat area.[35,36] Leptin is believed to be a potential mediator as it regulates TSH directly on the level of the paraventricular nucleus and indirectly on the level of the arcuate nucleus.[37] Both the hypothalamic-thyroid axis and leptin loop system are known to modify certain signaling processes in the hypothalamic nuclei.[38]

Hypothyroid status

Our findings corresponded with studies by Cabral *et al.* and Anil Regmi *et al.*[25,39] An increase in total cholesterol and LDL are attributed to the effect of thyroid hormone on a rate limiting enzyme in bile acid synthesis which promotes LDL oxidability.[40] Elevation of HDL is essentially due to the reduction of cholesteryl ester transfer protein and hepatic lipase activity.[41] However, Sangeeta *et al.* found an increase in cholesterol, LDL and TG among subclinical hypothyroidism and overt hypothyroidism patients whereas there was a decrease in HDL levels compared to normal thyroid status.[3] To date, no study was done regarding the correlation between TSH/free T4 and BMI or the percentage of total body fat among hypothyroidism subjects. However, generally, according to Adam S. *et al.*, changes in free T3 and free T4 and TSH were negatively correlated with changes in the body weight, fat, muscle and body water mass.[42] Changes in TSH were positively correlated with changes in body weight, fat, muscle and water masses. It was postulated that hypothyroidism induced weight gain mainly by increasing adiposity due to reduce low body energy demands and lower metabolism.[42]

Euthyroid status

A significant negative correlation between free T4 with the percentage of total body fat and BMI found among patients in this group. Based on Yun Zhang *et al.*, TSH was positively associated with T-Chol and LDL in euthyroid diabetic women as a consequence of autoimmune activation involving lipoprotein and oxidatively-damaged TSH.[43]

According to DanThyr *et al.*, no correlation between TSH and BMI and inverse correlation between free T4 and weight change in women.[44] Based on a longitudinal population study in normal-weight individuals for 9.8 years, the risk of having abnormal BMI (either overweight or obese) increased with the decrease in serum free T4, although no association was seen with a change in serum TSH.[45] Moreover, other studies showed a positive relationship between serum TSH and adiposity indices including BMI.[46] The difference between TSH and BMI was investigated under the influence of adipose tissue signals. The central regulation of thyroid hormone through thyroid releasing hormone (TRH) is produced by leptin. It is vital for the downward adjustment of excess energy.[7,32] A positive correlation between serum leptin and TSH has been found to suggest a positive correlation between BMI and TSH.[47] The transport, metabolism and

receptor binding of thyroid hormones and their impact on peripheral tissues are directed by circulating free T4 as well as the response of pituitary TSH to a deviating free T4 may not be log linear as the magnitude of the deviation decreases.[45,48] Based on a study among young men with euthyroidism, less favourable body composition with higher fat and lower muscle mass. They hypothesized that part of the effects of body fat on thyroid hormone concentrations was explained through thyroglobulin (TBG). TBG is a marker of nutritional status, expected to be higher in those with higher fat mass.[36] Another similar study showed no significant correlation between serum thyroid levels and body fat percentage.[49] Thyroid hormones impact body composition by changing the cellular metabolism from adenosine triphosphate (ATP) synthesis or changes in the metabolic process downstream from mitochondria.[49,50]

Confounding factor

One of the confounders was post-menopausal age that evidently showed a higher lipid profile due to the reduction of oestradiol. According to de Kat AC *et al*, at all ages between 46 and 55 years, naturally, postmenopausal women had 0.2 to 0.4 mmol/L higher TC and 0.1 to 0.3 mmol/L higher LDL levels compared to premenopausal women in the same age range. However, we neglected this factor as the increment was small and our main aim was to treat high fasting lipid profile or dyslipidaemia. Based on Chen Y *et al*, a reduction of LDL of 1.0 mmol/L was associated with a 22% decreased rate of major vascular events.

CONCLUSIONS

The significant correlation between dyslipidaemia and hypothyroidism is supported by the mechanism of lipoprotein transport in lipid metabolism. Hypothyroidism among patients with thyroid disorders carries a higher risk of a cardiovascular event by elevation of T-Chol. Therefore, lipid profile screening is beneficial and should be routinely performed among patients with thyroid disorders to monitor their cardiovascular risk. Even a small reduction of TG, T-Chol and LDL levels results in a significant reduction in cardiovascular morbidity. Regular assessment of lipid profiles among hypothyroid patients can prevent the progression of the disease to severity.

FUTURE RECOMMENDATION

A larger sample size is recommended to be conducted in a future study to ensure that a wider population for thyroid status disorder patients can be represented. The study group can be divided into subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism in view of it might yield different association or correlation.

CONFLICT OF INTEREST

The authors whose name listed in the paper has no financial, non-financial nor conflict of interest in the subject matter or materials discussed in this manuscript.

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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