

Original Article

The Relationship of Dyslipidemia with Retinopathy in Type 2 Diabetes Mellitus Patients with Subclinical Hypothyroid

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Abstract:

Background: Studies have shown type 2 diabetes mellitus (T2DM) accompanied by subclinical hypothyroid (SCH) leads to a higher retinopathy incidence, compared to T2DM without SCH. Furthermore, SCH patients are known to have a high risk of dyslipidemia. This study therefore aims to determine the relationship between dyslipidemia and retinopathy, in T2DM patients with SCH.

Materials and Methods: This study used a cross-sectional design, and the study population consisted of adult patients diagnosed with T2DM over a year ago and visiting the Metabolic Endocrine Division's outpatient ward at Cipto Mangunkusumo Hospital. The data collected include glycemic control, FT4, lipid profile TSHs, as well as retinopathy data.

Results: According to the results, patients with T2DM and SCH accompanied by dyslipidemia, had a 2.76 times higher retinopathy risk, compared to patients without dyslipidemia (p value = 0.014).

Conclusion: A significant relationship was concluded to exist between dyslipidemia and retinopathy in T2DM patients with SCH.

Keywords: *Subclinical hypothyroid, type 2 diabetes mellitus, dyslipidemia, and retinopathy.*

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Introduction

Hypothyroid disorder is quite a common endocrine disease in the society. A recent study showed subclinical hypothyroid disorder (SCH) is the most acquired thyroid disorder in T2DM.¹ SCH is defined as a state of increased concentration of serum thyroid stimulating hormone (TSH), with triiodothyronine (T3) and serum thyroxine (T4) within regular levels.^{2,3} The thyroid gland's function has been long known to be associated with fat metabolism, blood sugar homeostasis, and enzymes with a role in the lipoprotein circulation.⁴ Danforth *et al.*, first expressed the relationship between thyroid hormone production and carbohydrate consumption.⁵ In diabetic patients,

a decrease in thyroid hormone levels, compared to TSH occurs, leading to hypothyroid disorder.^{6,7} According to several studies, SCH is a risk factor for high blood cholesterol levels.^{12,13,14,15,16} Furthermore, the risk of dyslipidemia in SCH patients is much higher for patients above 60 years.¹⁷ Other studies have also shown the risk of dyslipidemia to increase in line with TSH levels.¹⁸ Apparently, the administration of therapy for hypothyroid (levothyroxine) to hypothyroid patients accompanied by dyslipidemia, is able to lower cholesterol levels and LDL, except in cases where other predisposition caused the rise in blood cholesterol.¹⁹ Previous studies recorded an average decrease in total cholesterol and LDL by about

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9-15 mg/dL and 11 mg/dL, respectively, in SCH patients undergoing levothyroxine therapy.^{20,21} In addition to the thyroid gland, TSH receptors also occur in the liver, indicating the role of thyroid hormones role in regulating liver function.²² These hormones inhibit cholesterol synthesis by rendering hydroxy-methylglutaryl coenzyme A (HMG-coA) reductase inactive, and also aid the liver in removing excess cholesterol in the blood. Subsequently, blood cholesterol moves to the bile and is excreted with feces. Thyroid hormones also have the effect of lowering intestinal cholesterol absorption. Therefore, a reduction in the level of this hormone levels impairs the liver's ability to cleanse excess fatty acids, blood triglycerides, and cholesterol. In addition, hypothyroid conditions stimulate the HMG-coA's activity, thus, increasing blood cholesterol.²² Based on previous studies, SCH patients are highly susceptible to the development of heart disease, due to disorders in vascular endothelial as well as increased blood cholesterol.²³ Meanwhile, other studies suggest hypothyroid patients having dyslipidemia accompanied with diabetes, are more prone to coronary heart disease and atherosclerosis, compared to non-diabetic counterparts.²⁴ Also, in patients without impaired insulin sensitivity, TSH increase is not necessarily accompanied by LDL cholesterol increase. Instead, the different conditions are obtained in the subject offering from insulin resistance, where a strong positive correlation exists between the increased TSH and high LDL cholesterol levels.

Meanwhile, retinopathy is a common microvascular complication in T2DM patients. In 2002, the World Health Organization (WHO) estimated 5% of the 37 million blindness cases worldwide to be caused by retinopathy.²⁵ Several factors, including chronic oxidative and inflammatory stress, as well as insulin resistance occurring in diabetic patients are known possible causes of retinal vascular endothelial cells.²⁶ However, not all diabetes patients with considerably high sugar levels have retinopathy as well. Conversely, counterparts with controlled blood sugar are also exposed to retinopathy, and this implies there are other factors influencing retinopathy incidence in T2DM patients. A previous study on T2DM patients suffering from retinopathy obtained average low-density lipoprotein (LDL) as well as total cholesterol levels and this was significantly higher, counterparts without retinopathy.²⁷ Interestingly, apart from glucose

control, controlling dyslipidemia by administering drug class statins or fibrates to T2DM patients successfully reduced the progress of retinopathy.²⁸ This indicates abnormalities of dyslipidemia have a possible role in the retinopathy process within these patients.

Furthermore, retinopathy complications often occur in SCH patients with T2DM. Insulin resistance in these patients lowers blood vessel dilation ability in the retina, causes fibrosis, and consequently, damages retina blood vessels to some extent.²⁴ Also, patients with SCH and diabetes, experience a rise in serum C-reactive protein (CRP), a marker of a non-specific inflammatory reaction within the body.²⁹ This inflammatory reaction causes endothelial cell damage to small retina blood vessels.³⁰ According to several experts, patients with diabetes and uncontrolled dyslipidemia require hypothyroid screening.^{31,32} Therefore, there is an important need to understand the factors influencing the severity of retinopathy. In this study, the risk factors to be examined are the serum lipid levels, comprising of total triglycerides, cholesterol levels, HDL and LDL levels.

Materials and Methods

The study sample is the same as our previous study titled "Proportion of Subclinical Hypothyroidism in Patients with Diabetes Mellitus" and has been already published.¹ The research design was cross-sectional, and the research subject were obtained from medical records and laboratory tests of diabetic patients admitted in the diabetic polyclinic, endocrine metabolic division, internal medicine department, Cipto Mangunkusumo, Hospital Jakarta between March and April, 2016. The parameters observed were triglyceride, serum, cholesterol, HDL, and LDL levels, while the study population comprised adult patients diagnosed with T2DM at least 1 year ago. In addition, the exclusion criteria was T1DM patients, pregnant women and patients treated with anti-thyroid or thyroid hormones, as well as other medications with possible effect on thyroid status. Subsequently, the data collected were analyzed using SPSS 16.0 program, and variables with P value <0.05 were designated as significantly related.

Results

Table 1 shows the populations bio-data for the two hundred and seventy-eight patients diagnosed with diabetes and studied. Based on the recent study on a total of 278 T2DM subjects, the number of patients with SCH amounted to 20 (7.2%).¹

Tabel 1. Basic characteristics of research subjects.

Characteristics	n (%)
Sex	
Male	128 (42.8)
Female	171 (57.2)
Age	
≥ 60 Years	140 (50.4)
< 60 Years	138 (49.6)
Occupations	
Unemployed	8 (2.9)
House wife	115 (41.4)
Retiree	89 (32.0)
Self employed	32 (11.5)
Private sectors	11 (4.0)
Government worker	23 (8.3)
Educations	
Uneducated	2 (0.7)
Grammar School	44 (15.8)
Junior High School	34 (2.2)
High School	118 (42.4)
Diploma degree	27 (9.7)
College degree	53 (19.1)
Family history for thyroid disease	
Yes	11 (4.0)
No	267 (96.0)

Table 2. The proportion of hypothyroid inpatients with type 2 diabetes

Variable	Total subject	SCH	Overt hypo thyroid	Euthyroid
	n	n	n	n
Total	278 (100)	20 (7.2)	2 (0.72)	256 (93.80)

Table 3. Relationship of dyslipidemia with the incidence of retinopathy in T2DM patients with SCH

Variable	Retinopathy		PR (IK 95%)	P
	Yes	No		
Dyslipidemia				
Yes	13	1	2,786	0,014
No	2	4	(0,890-8,718)	

*Analysis using the Fisher Exact test, significance if the P value is <0.05

Meanwhile, Table 2 shows the study results. This study assessed the proportion of dyslipidemia as well as retinopathy in T2DM patients with SCH.

Table 3 shows the results of Fisher Exact test, use to calculate the relationship between dyslipidemia and retinopathy incidence.

According to the study's results, 14 out of 20 subjects suffering from T2DM with SCH were discovered to have dyslipidemia, while the rest did not. Of these 14 subjects, 13 suffered from retinopathy as well. Table 5 shows the T2DM patients SCH and dyslipidemia have a 2.8 greater susceptibility to retinopathy, compared to counterparts without dyslipidemia ($p=0.014$).

Discussion

The socio-demographic factors of employment and education are not directly related to diabetes and thyroid disorders risks. However, the level of education is mostly primary institution to college, and this is useful in helping the subject understand questions posed during the interviews conducted. In employment, this variable is rarely discussed specifically due to the minute role in providing values for T2DM or thyroid disorder related research. Furthermore, majority of the subjects are housewives (41.4%), followed by retirees (32%), thus, the impact of occupation on the study's results are negligible. However, family history of thyroid abnormalities is quite important due to genetic risk in several thyroid disorders. In this study, only 11 subjects (4%) have a family history of thyroid disorders, thus, this factor's influence is also negligible.

Based on Table 1, the percentage of T2DM patients with SCH is 7.2%, while the hypothyroid overt is only 0.72%. A meta-analysis study by Han *et al.*,³³ showed T2DM is riskier in cases where the condition is accompanied by SCH. The values obtained in this study are lower, compared to the study in India (16.3%), but do not differ significantly from the study conducted in the Americas.³⁴ However, the percentage of overt hypothyroid is much lower, compared to SCH, and this is in accordance with the studies in India as well as America. According to these results, SCH does not have a typical clinical complaint, but requires special attention, considering the future risk of becoming hypothyroid overt. A study on SCH patients undergoing no treatment, followed for 10 - 20 years, showed 33-55% of the subjects were bound to develop clinical hypothyroid.³⁵ In this study, SCH incidence was more prominent in T2DM patients above 60 years, and there was no difference between the number of male and female SCH patients (Table 1). These results were in accordance with previous studies stating SCH's

risk increased to 20% at age over 60 years.¹⁹

Table 3 shows there is a 2.76 times higher susceptibility to retinopathy in T2DM patients with SCH as well as dyslipidemia, compared to counterparts without dyslipidemia. Dyslipidemia is common in diabetes and there is strong evidence that lowering blood glucose improves vessel abnormalities outcome.³⁶ The relationship between hypothyroid, dyslipidemia and blood vessel abnormalities was first reported in 1967.³⁷ Premature infants born before 27 weeks of pregnancy are often born with hypothyroid disorders, due to disruption in the thyroid and hypothalamic-pituitary axis.³⁸ These infants are therefore highly susceptible to premature retinopathy.³⁹

In experimental mice, hypothyroid has the capacity to cause impaired vascular permeability within the retina.⁴⁰ In addition, thyroid function screening is recommended by ATA only in children with T1DM. Meanwhile, for T2DM, there is currently no specific recommendation on the need for this screening. This is a possible cause of an undetectable SCH disorder at the beginning of an easily detectable new connection with a hypothyroid overt, due to the typical clinical symptoms. Therefore, SCH diagnosis is enforced using only laboratory values, in relation to the clinical symptoms of atypical SCH. According to the ATA recommendation, thyroid hormone therapy is administered in cases where the level of TSH above 10 mU/l, while TSH levels between 4-10 mU/l simply require observations. This is risky due to the chances of leading to therapy in thyroid disorders, particularly delayed SCH, because studies show 75% of SCH patients have TSH value below 10 mU/l. Based on other studies, administering thyroid hormones to young rats facilitates retina blood vessel development.³⁷

Table 3 shows most T2DM patients with SCH suffer dyslipidemia (14 out of 20 subjects). Several previous studies showed high SCH figures in dyslipidemia patients.^{38,39} Dyslipidemia is common in diabetes thus, patients with uncontrollable dyslipidemia disorders ought to undergo thyroid function screening. Subsequently, thyroid

hormone therapy ought to be administered in cases where a hypothyroid disorder is discovered, in order to treat the dyslipidemia.

This is the first study to report the relationship between T2DM, SCH, dyslipidemia and retinopathy. Furthermore, this study showing the percentage of T2DM patients with SCH in Indonesia, as prior research has been conducted abroad.

Limitation of the study: This study was conducted in only one National Diabetes Referral Hospital in Jakarta. Therefore, the results do not fully to represent the entire diabetes population in Indonesia. In addition, the study used a cross-sectional cut design, and is therefore not suitable for concluding a causal relationship as well as the direct result between the studied variables.

Conclusion and Recommendations

Based on this study, there is a relationship between dyslipidemia and the high retinopathy incidence recorded in T2DM patients with SCH. Therefore, preliminary research is required to be continued with the cohort study, and a wider population scale, to ensure all the results are suitable inputs for develop clinical recommendations related to early screening thyroid abnormalities, dyslipidemia and retinopathy in T2DM patients.

Conflict of interest: The authors declared that that were no conflicts of interest.

Ethical approval issue: This research has been approved by the University of Indonesia's research ethics committee. All data obtained and used in this study will be kept confidential.

Individual authors contribution: Idea owner of this study: HH, LAP, DSH, IS., Data gathering: HH, LAP, DSH, IS., Writing and submitting manuscript: HH, LAP, DSH, FNA, IS, SS., Editing and approval of final draft: HH, LAP, DSH, FNA, IS, SS.

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