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The proportion of Hypothyroid in Type 2 Diabetes Mellitus Patients in Dr. Hasan Sadikin Hospital

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) and thyroid dysfunction often coexist. Both diseases have overlapping pathomechanisms and increased risk along with advanced age. The prevalence of hypothyroidism in patients with T2DM is 12%-15% compared to 1.3%-4.6% of the general population. Glycemic control is an essential factor in developing hypothyroidism. Thyroid Stimulating Hormone (TSH) levels are used to diagnose hypothyroidism because subclinical hypothyroidism commonly shows normal T4 and T3 levels. This study aimed to measure TSH levels in patients with T2DM. The study design was observational, descriptive, and cross-sectional. Researchers carried out TSH measurements by using leftover samples from T2DM patients. Subjects were recruited by consecutive sampling. The inclusion criteria were subjects > 35 years old who were diagnosed with T2DM. The exclusion criteria were subjects who were previously diagnosed with hyperthyroidism or hypothyroidism. This study found that 11% of 71 subjects had elevated TSH levels. The subjects were 32 (45%) male and 39 (55%) female patients aged 38-72 years. Subjects with high TSH levels were between the ages of 49 and 72. There were 5 of 8 subjects (62.5%) with elevated TSH levels and poor glycemic control. The prevalence of hypothyroidism in T2DM was 11%. Thyroid stimulating hormone is recommended for T2DM, especially in patients over 50 with poor glycemic control.

Keywords: Hypothyroidism, stimulating thyroid hormone, diabetes, type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus and thyroid dysfunction are two endocrine disorders widely found in clinical practice and frequently coincide, have overlapping pathomechanisms, and the risk of both diseases is increased along with increased age.[1] Type 2 Diabetes Mellitus (T2DM) has a pathological basis related to thyroid dysfunction.[2] various studies have shown the prevalence of thyroid dysfunction in patients with T2DM was approximately 12%-15% compared to 1.3%-4.6% in the general population. Uncontrolled T2DM affects thyroid hormones, genetics, and biochemistry, and that may be the reason for the relationship between diabetes mellitus and hypothyroidism.[2,3] Reports suggest that T2DM causes subclinical hypothyroidism.[4] Subclinical hypothyroidism is characterized by an increase in Thyroid Stimulating Hormone (TSH), but T4 (thyroxine) and T3 (triiodothyronine) levels may still be within normal limits with or without symptoms.[4] Subclinical hypothyroidism is independently associated with severe diabetic retinopathy, and undiagnosed thyroid dysfunction in a patient with diabetes may affect their metabolic profile and thus increase the risk of diabetic complications.[1,5-7]

The low T3 state may be caused by apparent hyperglycemia, which reduces the peripheral conversion of T4 to T3 via mono-deiodination reactions.[8] It is known that insulin is an anabolic hormone that inhibits the hepatic conversion of T4->T3 and increases T4 levels, followed by decreased T3 levels. Type 2 diabetes mellitus is associated with increased insulin levels and C-peptide levels. Insulin is an anabolic hormone that increases TSH turnover. C-peptide has been shown to increase Na + / K + ATPase activity, which can also increase protein synthesis, leading to an increase in TSH turnover. Hyperglycemia in people with T2DM is known to harm thyroid function by impairing the pituitary TSH response to stimulation by the hypothalamus TRH. This process may be due to the post-translation changes in glycosylation of TRH affecting its biological activity.[8,9]

Timely screening for thyroid dysfunction, especially subclinical hypothyroidism, is essential as most cases are usually asymptomatic and can prevent severe diabetic complications. The incidence of thyroid dysfunction with subclinical hypothyroidism is characterized by an increase in the

TSH hormone.[6,10,11] the study aimed to measure TSH levels in patients with T2DM in the outpatient population.

METHODS

This research was conducted in the Central Laboratory of Clinical Pathology Hasan Sadikin Hospital, Bandung. The design of this study was a descriptive, cross-sectional study. The subjects of this study were patients diagnosed with T2DM based on American Diabetes Association (ADA) criteria at Dr. Hasan Sadikin Hospital from February 1 to July 31, 2020. Sampling was based on consecutive purposive sampling. Purposive sampling is a sample determination technique by selecting samples from the population according to consideration by authors (objectives/problems in research) to represent the population's characteristics that have been known previously. Contrastingly, consecutive sampling is a method that is carried out by selecting samples that meet the research criteria following the order of arrival until a certain period to meet the minimum sample size. Samples in this study were taken based on the inclusion and exclusion criteria. Subject inclusion criteria were patients > 35 years old diagnosed with T2DM. The patient exclusion criteria were T2DM patients previously diagnosed as hyperthyroid or hypothyroid. The sample's exclusion criteria were the remaining specimens that did not meet the requirements for laboratory tests, such as hemolysis, icteric or lipemic. The normal TSH levels per the insert kit are 0.2-8.1 IU/mL. Thyroid stimulating hormone value <0.2 IU/mL indicated a possibility of hyperthyroidism, while increased TSH level (TSH> 8.1 IU/mL) indicated a possibility of hypothyroidism. Thyroid stimulating hormone levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA) method with General Biological Cooperation (GBC) TSH kit from Taiwan and were read with a spectrophotometer (Rayto RT-6500) in the Central Laboratory of Clinical Pathology Dr. Hasan Sadikin Hospital, Bandung.

The formula to determine a minimum number of samples to obtain a significant number of diabetes patients in this study was as follows:

$$n = \frac{Z^2 pq}{d^2}$$

$$n = \frac{Z^2 p\,(1 - p)}{d^2}$$

Description:
n=the minimum number of samples required
Z=degree of confidence; 5%=1.96
p=proportion of patients with T2DM with thyroid dysfunction
q=1-p (proportion of T2DM patients without thyroid dysfunction)
d=limit of error or absolute precision

The proportion of dysfunctional thyroid patients with DM in a study by Talwalkar was 24.8%, indicating that the p-value = 0.248 and the q=1-p-value was 0.752. . The specified error limit (d) was 71, and the alpha value =0.05. Therefore, the number of samples needed in this study was:

$$n = \frac{1{,}96^2 . 0{,}248 . 0{,}752}{0{,}1^2} = 71$$

Based on these calculations, 71 samples must be added to the anticipation of a 10% data loss, resulting in a total sample size of 79. Therefore, the study received ethical approval from the Health Research Ethics Commission of Dr. Hasan Sadikin Hospital with number LB.02.01/X.6.5/218/2020.

RESULTS AND DISCUSSIONS

From February 1, 2020, to July 31, 2020, 79 T2DM patients with ages> 35 years old in the Outpatient Clinic in Dr. Hasan Sadikin Hospital were selected to investigate the relationship between T2DM and thyroid disease. A total of 8 samples were excluded consisting of 4 samples due to duplication and four samples due to the patient's age and the final diagnosis of type 1 diabetes. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of age, gender, HbA1c level, fasting blood glucose, 2-hour post-prandial glucose, and TSH levels (Table 1).

Table 1. Normality test

Criteria Group	Sig Value
Age (years)	0.200
HbA1c%	0.003
Fasting blood sugar levels (mg/dL)	<0.001
2-hour post-prandial blood sugar (mg/dL)	<0.001
TSH	<0.001

The Kolmogorov-Smirnov test value in Table 1 showed that age had a normal data distribution because the significant value was > 0.05. However, data on HbA1c, fasting blood glucose, 2-hour post-prandial blood glucose, and TSH levels were not normally distributed. Characteristics of subjects in this study, such as age, gender, HbA1c, fasting blood glucose, 2-hour post-prandial blood glucose, and TSH levels, can be seen in Table 2.

The study's results (Table 2) showed that the TSH hormone tended to increase above normal levels (11%), and no low TSH results were found in this study. The normal value used in this study was based on the reagent insert kit (0.2-8.1 IU/mL). According to a survey by Talwakar, 24.8% of T2DM subjects were affected by hypothyroidism in India, whereas a study by Ogbonna found hypothyroid with elevated TSH levels in 11,6% of T2DM subjects in Nigeria.[12,13] Diabetes can affect thyroid function by altering TSH levels and interfering with converting thyroxine (T4) to triiodothyronine (T3) in peripheral tissues.[10] Increased TSH levels and normal TSH were analyzed based on the characteristics of age, gender, HbA1c, fasting blood glucose, and 2-hour post-prandial blood glucose data in Table 3.

The average age of subjects with high TSH was 60 years, with a range of 49-72 years. Fasting blood glucose, 2-hour post-prandial blood glucose levels, and HbA1c was higher in subjects with increased TSH compared to subjects with normal TSH levels.

HbA1c was then used in this study to assess good or poor glucose control according to the PERKENI guidelines.[14] An HbA1c level > 8% indicates poor hyperglycemic control (Table 4).

It was illustrated in Table 3 that TSH was elevated in subjects with HbA1c < 8 or good control of hyperglycemia was reported in 3 out of 8 patients (38%). There were 5 out of 8 patients (62%) whose elevated TSH levels and poor control of glycemia. Patients with normal TSH but had reasonable hyperglycemic control were 34 out of 63 patients (54%). However, 29 patients (46%) had normal TSH levels but poor hyperglycemic control. Altered thyroid hormones have been described in patients with diabetes, especially those with poor glycemic control. The nocturnal TSH peak levels in diabetic patients are impaired, thus impairing TSH response to Thyroid Releasing Hormone (TRH). Reduced T3

Table 2. Subject characteristics and TSH levels

Subject Characteristics (n)	Total
Age (years), mean (±SD)	56.9 (±8)
Age range	38-72
Gender	
Male n (%)	32 (45)
Female n (%)	39 (55)
HbA1c%, median (range)	8 (5.7-12.5)
Fasting blood sugar levels mg/dL, median (range)	167 (101-397)
2-hour post-prandial blood sugar mg/dL, median (range)	228 (119-621)
TSH μIU/mL, median (range)	2.96 (0.23-27.95)

Table 3. Characteristics of subjects with increased and normal TSH levels

Subject Characteristics (n)	High TSH (N=8)	Normal TSH (N=63)
Number of subjects (%)	11%	89%
Age (years), mean (±SD)	60(±8)	56.4 (±8)
Range	49-72	39-72
Gender		
Male (%)	75	41
Female (%)	25	59
HbA1c%, median (range)	8.6 (6.9-12.3)	7.9 (5.7-12.5)
Fasting blood sugar levels mg/dL, median (range)	168 (127-392)	171 (95-397)
2-hour post-prandial blood sugar mg/dL, median (range)	264 (151-446)	215 (69-621)

Table 4. Comparison of TSH and HbA1c among research subjects (n=71)

Variable/Group	HbA1c <8%	HbA1c ≥8%	Total
Normal TSH	32	31	63
High TSH	3	5	8
Total	35	36	71

levels have been observed in uncontrolled diabetic patients. An impairment could explain this "low T3 state" in the peripheral conversion of T4 to T3 that normalizes with improved glycemic control.[12,15] This study's proportion of elevated TSH to elevated HbA1c was not statistically significant based on the Chi-Square test (p-value 0.502). This finding might be due to the small number of samples of high TSH compared to normal TSH. A study by Ogbonna only found 11.6% of T2DM subjects with elevated TSH.[13]

There were higher numbers of subjects with elevated TSH whose poor hyperglycaemic control (HbA1c>8) compared to those with good hyperglycemic control. A study by Khassawneh on 1341 patients in Jordan showed that serum T4 levels, T3 levels, basal TSH levels, and TSH responses to TRH were strongly influenced by glycemic control.[15] The longer duration of diabetes and older age increase the risk of developing hypothyroidism. The American Thyroid Association recommends that adults be screened for thyroid dysfunction by measurement of the serum TSH levels, starting from age 35 years and every five years after that. At the same time, high-risk patients may require more frequent testing (annually).[10,15]

The glycemic effects take a long time to cause thyroid dysfunction or endocrinopathy. Thyroid-stimulating hormone changes in T2DM patients are not as fast as changes in HbA1c levels in these patients. This fact explains how HbA1c > 8 but TSH remained normal or vice versa.

There was no data on the length of illness in this study, only the duration of treatment at Dr. Hasan Sadikin Hospital. This finding was because this research was based on laboratory-based data. This research was initially planned to be completed in 3 months; however, due to the pandemic, researchers extended the duration of the study to 6 months for enough research samples. As a result, the number of visits to T2DM patients to the hospital decreased during the pandemic situation of COVID-19.

CONCLUSIONS AND SUGGESTIONS

It was found in this study that the prevalence of hypothyroidism based on TSH levels for T2DM patients was 11%. Type 2 DM subjects with poor glycemic control and older age have an increased risk of hypothyroidism because age affects thyroid function. It was suggested to perform follow-up research based on clinical status and annual screening of hypothyroidism in patients over 50 years old, especially those whose poor glycemic control. Initial screening for hypothyroidism was carried out using TSH measurement. Abnormal TSH results must proceed with the measurement of serum-free T4 levels.

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