

# **LAMPIRAN**

## Lampiran 1



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### **Thyroid dysfunction in type 2 diabetics seen at the University College Hospital, Ibadan, Nigeria**

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**Summary:** Thyroid dysfunction complicates the metabolic derangement observed in Diabetes Mellitus (DM). It is necessary to recognize and treat it when present in order to achieve stability of metabolic control in these patients. The prevalence of thyroid dysfunction in type-2 diabetics in our environment is not known. This study was therefore designed to determine the prevalence of thyroid dysfunction in Type 2 diabetics seen at the Metabolic Research Unit of University College Hospital, Ibadan, Nigeria. Serum TSH, Free T3 & Free T4 assays were performed using Automated Enzyme Immunoassay platform on fresh sera from volunteers comprising 64 adult type 2 diabetics and 36, age matched, non diabetic controls; weight, height and blood pressures were measured in all subjects. In addition, past lipid profile results of type 2 diabetics were retrieved from medical records. Thyroid dysfunction was present in 19 (29.7%) of 64 type 2 diabetics and 1 (2.8%) of 36 non diabetic controls ( $P < 0.05$ ). The prevalence of thyroid dysfunction is 32.4% in females and 25.9% in males. Secondary hypothyroidism was seen in 78.9%, sub-clinical hypothyroidism in 15.8%, and sub-clinical hyperthyroidism 5.2% of subjects with thyroid dysfunction. Abnormal lipid profiles were seen in 35.4% of euthyroid type 2 diabetics and 100% of hypothyroid type 2 diabetics ( $P < 0.05$ ). 87.5% of type 2 diabetics and 38.8% of controls were hypertensive ( $P < 0.05$ ). 7.8% of type 2 diabetics and 50% of controls were obese ( $P < 0.05$ ). The prevalence of thyroid dysfunction in type 2 is higher in type 2 diabetics than in controls. More of Type 2 diabetics were obese and more of them were hypertensive compared to controls. The approach of using TSH first in screening for thyroid dysfunction is not sufficient in type 2 diabetics. Routine screening for thyroid dysfunction should be carried out in type 2 diabetics.

**Keywords:** Thyroid dysfunction, Diabetes, Ibadan, Nigeria

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#### **INTRODUCTION**

Thyroid dysfunction is a spectrum of disorders of the thyroid gland which manifests either as hyper - or hypothyroidism and is reflected in the circulating levels of thyroid stimulating hormone (TSH) (Tunbridge et al, 1977).

Thyroid hormones, namely Tri-iodothyronine (T3) and Thyroxine (T4); either or both of which may be elevated or reduced have both direct and indirect effects on blood glucose homeostasis (Udiogong et al., 2007). Elevated levels of free circulating thyroid hormones (hyperthyroidism) produce hyperglycaemia by causing polyphagia, enhancing glucose absorption from the gastro-intestinal tract, accelerating insulin degradation and stimulating glycogenolysis (Loeb, 1996). Reduced levels of the hormones (hypothyroidism) may cause hypoglycaemia (Loeb, 1996; Cooper, 2003).

The prevalence of thyroid dysfunction is higher in diabetics than in controls. This has been estimated to be between 10 to 15% in diabetes compared to 6% in the non-diabetic population (Wu, 2000; Johnson, 2006; Udiogong et al, 2007). Numerous studies reported and justified this finding in type 1 diabetics (Cardoso et al., 1995; Wu, 2000; Sherman and Gagel, 2005;

Johnson et al., 2006) and only two studies reported the same finding in type 2 diabetics (Perros et al., 1995; Radaideh et al, 2004).

Although autoimmunity, in which circulating antibodies exist to numerous body tissue components destroy such tissues was stated to be the underlying mechanism behind the increased prevalence of thyroid disorders in type 1A diabetes (Hawa et al, 2006), despite the fact autoimmune thyroid diseases are known to be highly prevalent in all forms of diabetes; no specific reason has been adduced for an increased prevalence of thyroid disorders in antibody negative (type 1B) or type 2 diabetics (Wu, 2000; Radaideh et al, 2004). However, insulin; the hormone required for transporting glucose from plasma across cell membranes into the cytosol of many cells (including those of the skeletal muscle) is absolutely deficient in type 1 diabetics and relatively deficient in type 2 diabetics. Some authors have postulated that insulin treatment in type 1 diabetics and insulin resistance with resultant high plasma insulin levels in type 2 diabetes may equally predispose both groups to deranged thyroid function (Radaideh et al, 2004; Udiogong et al 2007; Pasupathi et al, 2008).

Type 2 diabetes is reported in association with hypothyroidism in the rare Crow-Fucase syndrome

*Mardianto, Suherdy dan Dharma Lindarto; Gambaran Fungsi Hormon Tiroid Pada Penderita DM Tipe 2 Rawat Jalan*

## **Gambaran Fungsi Hormon Tiroid Pada Penderita DM Tipe 2 Rawat Jalan**

**Mardianto, Suherdy, Dharma Lindarto**

### **Abstract**

**Background:** In previous studies reported that impaired of thyroid function in patients with type 2 diabetes showed different results. This study aims to know the description of the thyroid hormone function in type 2 diabetes mellitus outpatient.

**Methods:** A cross sectional study was conducted from September 2009 - March 2010 in H. Adam Malik General Hospital. The subjects were all outpatients at the clinic of Endocrine and Metabolic who met the criteria participated in this study. All samples were examined of TSHs, FT4, adrandon blood glucose, Total cholesterol, HDL cholesterol, and LDL cholesterol.

**Results:** There were 40 patients with type 2 diabetes who had participated in study with 19 men (47.5%), and 21 women (52.5%) with mean age of 58.3 years. We found thyroid dysfunction is 10% or 4 people and in details, 2 people (5%) of subclinical hypothyroidism and 2 people (5%) of subclinical hyperthyroidism. There were significant differences in average concentrations of three TSHs groups ( $p_1 = 0.0010$ ,  $p_2 = 0.012$ ,  $p_3 = 0.001$ ), whereas FT4 significantly different in eutrioid group and subclinical hyperthyroidism ( $p_2 = 0.001$ ) and subclinical hypothyroidism group and subclinical hyperthyroidism ( $p_3 = 0.001$ ). TSHs levels correlated positively and statistically significant with total cholesterol ( $r = 0.989$ ,  $p = 0.011$ )

**Conclusions:** Overview of thyroid hormone function in 40 patients with type 2 diabetes mellitus indicates 10% of dysfunction with more women than men, and ages who have been affected is over 60 years.*(JKS 2010; 1: 1-8)*

**Keywords:** *Dysfunction of Thyroid Hormone, Diabetes Mellitus Type 2*

### **Pendahuluan**

Diabetes melitus merupakan sindroma klinik yang ditandai dengan hiperglikemi disebabkan defisiensi sekresi insulin relatif atau absolut disertai dengan atau tanpa gangguan kerja insulin (resistensi insulin). Dari seluruh kasus diabetes lebih dari 90% adalah diabetes melitus tipe 2 (DM tipe2). Bukti-bukti klinik menunjukkan keadaan hiperglikemi adalah faktor utama penyebab terjadinya komplikasi kronik diabetes melitus baik mikrovaskular dan makrovaskular.<sup>1,2</sup>

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*Mardianto, Suherdy dan Dharma Lindarto adalah dosen pada bagian Ilmu Penyakit Dalam Universitas Sumatera Utara*

Data epidemiologi menunjukkan kecenderungan peningkatan jumlah kasus dari DM tipe 2 baik di dunia maupun di Indonesia. Pengendalian kadar gula darah adalah kunci dalam mencegah dan memperlambat komplikasi serta memperbaiki kualitas hidup pasien diabetes. Faktor-faktor yang mempengaruhi adalah penyerapan glukosa pada saluran cerna, glukoneogenesis dan glukogenolisis di hati, penggunaan glukosa oleh otot, sekresi insulin.<sup>1,3</sup> Adanya peranan hormon lain yaitu hormon tiroid yang mempengaruhi metabolisme karbohidrat termasuk juga insulin baik pada kadar hormon tiroid yang meningkat atau menurun, sehingga juga akan berpengaruh terhadap metabolisme glukosa pada DM tipe 2.<sup>4-6</sup>

## Thyroid Disorders in Patients of Type 2 Diabetes Mellitus

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**Abstract** The study was planned to assess the prevalence of thyroid disorders in type 2 diabetes in North Indian population and to correlate the serum insulin and glycosylated haemoglobin levels with thyroid hormones. It is a case control study. One hundred and twenty patients of type 2 diabetes were included in the study along with 117 adults of the same age group and normal glucose levels as controls. All blood samples were taken from subjects who fasted for at least 12 h before the blood collection. Glycosylated hemoglobin was determined by ion exchange chromatography and serum insulin and thyroid hormones were assessed through enzyme linked immunosorbent assay. Fasting blood glucose and glycosylated haemoglobin levels were significantly higher in diabetics showing a poor glucose control. Serum tri-iodothyronine values were significantly lower in diabetics. There was a significant correlation between glycosylated haemoglobin and thyroid hormones. There was no correlation between serum insulin and thyroid hormones.

**Keywords** Glycemic control · Thyroid hormones · Glycosylated haemoglobin · Insulin · Endocrine disorders · Hypothyroidism · Hyperthyroidism

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### Introduction

Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. Diabetes and thyroid disorders have been shown to mutually influence each other and an association between both conditions has been reported in literature [1]. Thyroid disease is a pathological state that can adversely affect glycemic control in diabetics and has the potential to affect the health. Thyroid disease is found commonly in diabetes and is associated with advanced age, particularly in type 2 diabetes and underlying autoimmune disease in type 1 diabetes [2].

Insulin and thyroid hormones are intimately involved in cellular metabolism and thus excess or deficit of either of these hormones result in the functional derangement of the other. The physiological and biochemical interrelationship between insulin and the influence of both insulin and iodothyronines on the metabolism of carbohydrates, proteins and lipids are recorded. Such records indicate that iodothyronines are insulin antagonist with high levels being diabetogenic while absence of the hormone inhibits the development of diabetes [3]. The thyroid hormone replacement is associated with a decrease in glycosylated haemoglobin (HbA1c) level, which is influenced by increased erythropoiesis rather than by changes in glucose level [4].

There is loss of vision in patients of graves disease who have superimposed diabetes and insulin resistance increases the nodularity of thyroid gland. Furthermore, it seems that unidentified thyroid dysfunction could negatively impact diabetes and its complications [1].

Excessive thyroid hormones increase the rate of digestive tract absorption and increase insulin resistance and insulin degradation. In hypothyroidism, liver secretion of

## Research Article

# Risk Factors for Thyroid Dysfunction among Type 2 Diabetic Patients in a Highly Diabetes Mellitus Prevalent Society

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Diabetes and thyroid dysfunction found to exist simultaneously. In this regard, the present study looked into the prevalence of different forms of thyroid dysfunction and their risk factors among Type 2 diabetic Saudi patients. *Methodology.* A cross-sectional retrospective randomized hospital-based study of 411 Type 2 diabetic Saudi patients of >25 years of age was conducted to test the prevalence of different types of thyroid dysfunction and their risk factors. *Results.* The prevalence of different types of thyroid dysfunction is 28.5%, of which 25.3% had hypothyroidism, where 15.3%, 9.5%, and 0.5% are clinical, subclinical, and overt hypothyroidism, respectively. The prevalence of hyperthyroidism is 3.2%, of which subclinical cases accounted for 2.7% and overt hyperthyroidism accounted for 0.5%. Risk factors for thyroid dysfunction among Saudi Type 2 diabetic patients are family history of thyroid disease, female gender, and duration of diabetes of >10 years, while the risk was not significant in patients with history of goiter and patients aged >60 years. Smoking and parity show a nonsignificant reduced risk. *Conclusion.* Thyroid dysfunction is highly prevalent among Saudi Type 2 diabetic patients, and the most significant risk factors are family history of thyroid disease, female gender, and >10 years duration of diabetes.

## 1. Introduction

Diabetes mellitus and thyroid dysfunction are the most common endocrine diseases seen in the adult population [1], while insulin or thyroid hormones metabolism can result in functional abnormalities of one another. The strong link between diabetes and thyroid diseases encouraged the American Diabetes Association (ADA) to propose that people with diabetes must be checked periodically for thyroid dysfunction [2]. Thyroid disease should be screened annually in diabetic patients to detect asymptomatic thyroid dysfunction [3]. At the same time, patients with thyroid dysfunction may need to be tested for the possibility of abnormal glucose metabolism, since excessive thyroid hormones cause increased glucose production in the liver, rapid absorption of glucose through the intestine, and increased insulin

resistance [4]. The thyroid gland is one of the endocrinal systems of the human body and can be affected by sustained hyperglycemia and the continuous endeavors by the body to correct for this carbohydrate imbalance. Studies have shown that diabetes and thyroid dysfunction can be found to exist together where thyroid disease can affect glucose metabolism and the untreated thyroid dysfunction can affect the management of diabetes [3, 5]. The association of the two endocrinal dysfunctions has been reported in different societies throughout the last two decades [6–8]. Diabetic patients have susceptibility to different types of thyroid dysfunction, whether hypothyroidism or hyperthyroidism; at the same time, patients with thyroid dysfunction are susceptible to suffer from either Type 1 diabetes or Type 2 diabetes [1, 9].

## Original Article

# Prevalence of subclinical thyroid disorders in type 2 diabetes mellitus

### Abstract

**Background:** Subclinical thyroid disorders usually do not produce symptoms of thyroid disease until they turn into overt thyroid disease. Thyroid disease is more common in people with diabetes mellitus than in the general population and it is important to detect thyroid disorder before its clinical manifestation. Subclinical hypothyroidism (SCH) can produce dyslipidemia, obesity thus resulting increased predisposition to coronary artery disease. Subclinical hyperthyroidism can aggravate hyperglycemia and impair blood sugar control. **Objectives:** Our objective is to determine the prevalence of subclinical thyroid disorders in patients with type 2 diabetes mellitus (T2DM) and to analyze the clinical and metabolic profile of patients with this dual endocrine disorder. **Methods and Results:** One hundred consecutive type 2 diabetic patients without clinical manifestations of thyroid disorders were screened for SCH and subclinical hyperthyroidism using serum free T<sub>3</sub>, free T<sub>4</sub> and thyroid stimulating hormone (TSH) levels. Individuals of subclinical thyroid disease were further screened for thyroperoxidase (TPO) antibodies. SCH was detected in 13% of type 2 diabetic patients and none had subclinical hyperthyroidism in our study. SCH was common among females with type 2 diabetes (84.6%). Elevated TPO antibody levels were present in 84.6% SCH patients. Diabetic retinopathy among SCH patients showed significant association with higher serum TSH levels. Left ventricular diastolic dysfunction was present in 30.8% of SCH patients. **Conclusion:** SCH is common among type 2 diabetic patients, especially in females. It is most commonly secondary to autoimmune thyroid disease. Microvascular complications are commonly observed in this group of patients with dual endocrinological disorder and treating physician should be aware of the impact and should routinely screen SCH to prevent complications.

**Key words:** Anti-thyroperoxidase antibody, diabetic retinopathy, left ventricular diastolic dysfunction, subclinical hypothyroidism, subclinical hyperthyroidism, type 2 diabetes mellitus

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## INTRODUCTION

The prevalence of thyroid disease in the diabetic patients is significantly higher than in the general population.<sup>[1]</sup> Apart from autoimmune etiology linked to the higher prevalence of thyroid disease in diabetes mellitus; it has also been observed that thyroid function is intrinsically linked to insulin resistance. It has also been stated that common factors simultaneously are responsible for increased thyroid stimulating hormone (TSH) levels and insulin resistance.<sup>[2]</sup>

In type 2 diabetes mellitus (T2DM), prevalence of thyroid disease has been found to be as high as 31%, the most common disorder being subclinical hypothyroidism, followed by subclinical hyperthyroidism, overt hypothyroidism and overt hyperthyroidism.<sup>[3]</sup> Subclinical hypothyroidism (SCH) is defined as a serum TSH level above normal despite normal levels of serum free thyroxine.<sup>[4,5]</sup>

SCH, in various studies, has been shown to be associated with elevation in serum lipids, coronary artery disease and left ventricular (LV) diastolic dysfunction, LV systolic dysfunction with exercise, increased peripheral vascular resistance and mental depression.

### Objectives

1. To determine the percentage of subclinical thyroid disorders in patients with T2DM.
2. To study the clinical and metabolic profile of patients with this dual endocrine disorder.

## Evaluation of hypothyroidism as a complication in Type II Diabetes Mellitus

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### Abstract

**Diabetes mellitus (DM) and Thyroid dysfunction, the two endocrine disorders have found to influence each other. The effects of which are poorly understood.** Therefore, the present study was undertaken to understand the association trend of thyroid dysfunction with diabetic process and to assess the hyperglycemic effect by correlating fasting serum glucose (FSG) and thyroid profile parameters. 58 type 2 DM patients were studied for their thyroid profile along with their fasting glucose levels. Analysis was performed by comparing the values with age and gender matched controls using student 't' test. Analysis showed that in type 2 diabetes mellitus patients, 7 (12.06%) patients had hypothyroidism and 18 (31.03%) subjects had subclinical hypothyroidism out of 58 subjects. Serum T3 and T4 hormone concentrations were low and Thyroid Stimulating Hormone (TSH) concentrations were high in Type 2 DM when compared to controls. But significant difference was found with T4 and TSH only (p value : <0.001). FSG did not show significant correlations with thyroid profile parameters. Type 2 Diabetes Mellitus patients are at risk for hypothyroidism and hence have to be followed up with serum TSH levels.

**Key words:** Diabetes mellitus, Hypothyroidism, Thyroid Stimulating Hormone (TSH)

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### Introduction

Diabetes mellitus the common heterogeneous endocrine disorder is rising in India and has reached approximately 20% in urban populations and approximately 10% in rural populations. [1] Diabetes mellitus on long term is associated with vascular complications that are responsible for increased morbidity and mortality among diabetic subjects [2]. New addition to these complications is the thyroid dysfunction which is indicated by the recent studies. [3] Thyroid dysfunction is increasingly found in the diabetes mellitus patients, the prevalence of which is around 13.4%. [4] Diabetes may affect the thyroid function to variable extent and unrecognized thyroid dysfunction not only worsens the metabolic control but also impede the management of diabetes. [5] Also, studies have suggested that type 2 diabetic patients with subclinical hypothyroidism are at risk of complications like nephropathy and cardiovascular events. [6] Therefore, diabetes patients need to be screened for thyroid dysfunction. Therefore, the present study was intended to evaluate the association

trend of thyroid hormone dysfunction with diabetic process and to assess the hyperglycemic effect by correlating fasting serum glucose and thyroid profile parameters.

### Materials and Methods:

This study was undertaken by the Department of Pharmacology, Sri Siddartha Medical College, Tumkur after the approval of the research and ethical committee. NIDDM patients attending the OPD of the hospital were tested for their fasting blood glucose (FSG), T3, T4 & Thyroid Stimulating Hormone (TSH). Diagnosed NIDDM patients constituting 58 in number with more than 5 years of duration and without the complications like retinopathy, neuropathy and nephropathy were selected. Similar numbers of age matched healthy volunteers were chosen as controls. Both cases and controls were non alcoholic, non smokers and non hypertensives. Diabetics were not associated with other endocrinological or non-endocrinological disorders and were on oral hypoglycemic agents. A total of 116 subjects were studied. Fasting se-

## The Relationship Between Thyroid Function and the Prevalence of Type 2 Diabetes Mellitus in Euthyroid Subjects

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**Purpose:** Thyroid hormones (THs) are primarily responsible for the regulation of energy balance and metabolism, suggesting that TH levels may contribute to the development of type 2 diabetes mellitus (T2DM). However, few studies have investigated the relationship between TH and T2DM in a general population. The aim of this study was to evaluate whether serum TH levels within the reference range are related to T2DM.

**Methods:** A cross-sectional study ( $n = 15,296$ ) was performed in Tianjin, China. Serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) levels were measured by chemiluminescence immunoassay, and T2DM was defined according to the American Diabetes Association criteria. Multiple logistic regression models were used to assess the sex-specific relationships between FT3, FT4, FT3/FT4 ratios, and TSH quintiles and T2DM.

**Results:** The prevalence of T2DM was 16.2% in males and 7.7% in females. In males, the multivariable-adjusted odds ratios (95% confidence interval) of T2DM for increasing quintiles of FT3, FT4, and FT3/FT4 ratios were 1.00, 0.75(0.63 to 0.89), 0.70(0.58 to 0.84), 0.63(0.52 to 0.76), 0.56 (0.46 to 0.68;  $P$  for trend < 0.0001); 1.00, 1.05(0.87 to 1.27), 1.16(0.96 to 1.40), 1.09(0.90 to 1.31), 1.29 (1.07 to 1.56;  $P$  for trend = 0.01); and 1.00, 0.69(0.58 to 0.83), 0.72(0.60 to 0.86), 0.59(0.48 to 0.71), and 0.55(0.46 to 0.66;  $P$  for trend < 0.0001), respectively. Similar results also were observed in females. In contrast, a strong negative correlation between TSH and T2DM was observed in males, but not in females.

**Conclusions:** This study demonstrated that decreased FT3, FT3/FT4 ratios, and increased FT4 levels are independently related to a higher prevalence of T2DM in both males and females, and TSH is inversely related to T2DM in males only. (*J Clin Endocrinol Metab* 102: 434–442, 2017)

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Type 2 diabetes mellitus (T2DM) is the most common chronic endocrine disease, characterized by hyperglycemia resulting from impaired insulin secretion and/or insulin resistance (1). The long-term complications of T2DM can significantly increase the risks of cardiovascular disease (CVD) and cancer, among many other

diseases, as well as significantly increase risk of mortality (2, 3). The global prevalence of diabetes mellitus is rapidly increasing due to an ageing population, urbanization and associated lifestyle changes. In 2013, an estimated 382 million people worldwide had diabetes mellitus, about 90 to 95% of whom had T2DM, and the

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Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; FT3, free triiodothyronine; FT4, free thyroxine; LDL, low-density lipoprotein; OR, odds ratio; SD, standard deviation; T2DM, type 2 diabetes mellitus; T3, triiodothyronine; T4, thyroxine; TC, total cholesterol; TG, triglyceride; TH, thyroid hormone; TSH, thyroid-stimulating hormone.

 Open Access Full Text Article

## ORIGINAL RESEARCH

# Prevalence of hypothyroidism in patients with type 2 diabetes mellitus and hypertension in India: a cross-sectional observational study

This article was published in the following Dove Medical Press journal:  
*Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*

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**Purpose:** To determine the prevalence of hypothyroidism in patients with type 2 diabetes mellitus (T2DM), hypertension, and both T2DM and hypertension (T2DM + hypertension) in India.

**Patients and methods:** In this cross-sectional observational study, adult patients with an established or newly diagnosed T2DM, hypertension, and T2DM + hypertension who were visiting their physicians for a routine clinical checkup were enrolled across 29 sites in India. All the patient-related data were extracted from their medical records. The prevalence of hypothyroidism was evaluated by thyroid function test (levels of serum free thyroxine, free triiodothyronine, and thyroid-stimulating hormone [TSH]). The proportion of obese and overweight hypothyroid patients and dose of thyroxine in overt and subclinical hypothyroidism (SCH) cases (as per TSH values) were assessed during the study. The results were summarized by descriptive statistics.

**Results:** A total of 1,508 patients (T2DM: 504; hypertension: 501; T2DM + hypertension: 503) were enrolled in the study. The prevalence of hypothyroidism in patients with T2DM, hypertension, and T2DM + hypertension was 24.8%, 33.5%, and 28.9%, respectively. The overall prevalence of hypothyroidism in T2DM (n=1,002) and hypertension (n=1,001) was 26.9% and 31.2%, respectively. The proportion of obese against overweight hypothyroid patients was higher in all indications (T2DM: 16.5% vs 3.4%; hypertension: 23.8% vs 5.4%; T2DM + hypertension: 21.5% vs 3.8%). A considerable proportion of patients with SCH was prescribed thyroxine in T2DM (61.5%), hypertension (61%), and T2DM + hypertension (62.5%) cases. The most commonly prescribed dose (mean) of thyroxine was 50 and 25 µg for overt hypothyroidism and SCH cases, respectively, in all cohorts.

**Conclusion:** There is a high (>20%) prevalence of hypothyroidism in patients with T2DM, hypertension, and T2DM + hypertension. Screening for hypothyroidism should be routinely considered for early diagnosis and effective management.

**Keywords:** hypertension, hypothyroidism, prevalence, type 2 diabetes mellitus

## Introduction

Hypothyroidism is a decreased functioning of thyroid gland. It can present itself as an overt state of myxedema, end-organ effects, and multisystem failure or subclinical condition with normal levels of thyroxine and triiodothyronine and mildly elevated levels of serum thyrotropin.<sup>1</sup> The prevalence of hypothyroidism was documented in ~4%–5% of population in the developed world, while in Indian population it was reported in around one in ten adults.<sup>2,3</sup>

Type 2 diabetes mellitus (T2DM) and hypertension have an intersecting underlying pathology with hypothyroidism. Various studies have shown a high prevalence of thyroid

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## Prevalence of thyroid dysfunction among Type 2 Diabetic Patients

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### Abstract

**Background:** Hypothyroidism is prevalent in patients with type 2 diabetes mellitus (DM).

**Objectives:** To assess the prevalence and the factors associated with hypothyroidism among type 2 DM patients.

**Subjects and methods:** A retrospective cohort study design was applied through record reviewing of type 2 diabetic patients at the Armed Forces Hospital, Southern Region (AFHSR), Khamis Mushayt, Saudi Arabia. All type 2 diabetics registered at the Diabetes Center of the AFHSR constituted the study population. A data collection sheet was used, which included personal characteristics, diabetes assessment, thyroid function assessment, and other possible risk factors.

**Results:** The study included 251 type 2 diabetic patients. Their mean age was  $38.6 \pm 23.5$  years with 39.6% of them aged 50 years or more. Slightly more than half of participants (52.4%) were females. Uncontrolled diabetes, manifested by having HbA1c  $\geq 7\%$ , was observed among 60.4% of patients. The mean duration of diabetes was  $11.1 \pm 7.49$  years. Thyroid disease was reported among 14.8% of type 2 diabetics. None of them reported family history of thyroid dysfunction. Factors significantly associated with thyroid disorders were female gender, ( $p=0.007$ ), obese patients ( $p=0.014$ ), being treated with oral hypoglycemic agents and insulin or insulin alone ( $p=0.049$ ).

**Conclusion:** A considerable proportion of type 2 diabetic patients have thyroid dysfunction. Screening for early detection of thyroid dysfunction in patients with type 2 diabetes mellitus should be done routinely in all places taking care of those patients in Khamis Mushait.

**Key words:** Type 2 Diabetes, Hypothyroidism, Risk factors, Saudi Arabia.

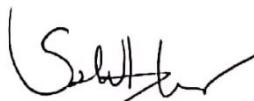
Lampiran 2

KARTU KONSULTASI

Nama Mahasiswa : I Gusti Putu Dicky Saputra  
Judul KTI : Gambaran Disfungsi Tiroid Pada Penderita Diabetes Mellitus Tipe 2  
Pembimbing Utama : Siti Aminah, S.Pd.,M.Kes

No.	Tanggal Bimbingan	Kegiatan	Paraf
1	23 desember 2020	Perbaikan BAB I dan BAB II	✓
2	11 Januari 2021	Perbaikan BAB I	✓
3	19 Februari 2021	Perbaikan BAB I, BAB II dan BAB III	✓
4	12 maret 2021	Perbaikan Judul , BAB I	✓
5	16 maret 2021	Perbaikan BAB I dan BAB II	✓
6	19 maret 2021	Perbaikan BAB I	✓
7	19 maret 2021	Perbaikan BAB I	✓
8	19 maret 2021	ACC, Seminar	✓
9	9 juni 2021	Bimbingan Setelah Sempro	✓
10	14 juni 2021	Bimbingan Setelah Sempro	✓
11	15 juni 2021	Bimbingan Setelah Sempro	✓
12	15 juni 2021	ACC, Perbaikan proposal	✓
13	24 juni 2021	Bimbingan BAB 4 dan 5	✓
14	23 juli 2021	Bimbingan BAB 9 dan 5	✓
15	26 juli 2021	ACC . Seminar hasil	✓
16	2 Agustus 2021	Bimbingan Setelah Semhas	✓
17	4 Agustus 2021	ACC, Cetak	✓

Ketua Program Studi  
Teknologi Laboratorium medis  
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## KARTU KONSULTASI

Nama Mahasiswa

: I Gusti Putu Dicky Saputra

Judul KTI

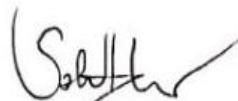
: Gambaran Disfungsi Tiroid Pada Penderita Diabetes Mellitus Tipe 2

Pembimbing Pendamping

: Wimba Widagdho Dinutanayo, S.ST.,M.Sc

No.	Tanggal Bimbingan	Kegiatan	Paraf
1.	31 desember 2020	Bimbingan BAB 1	/
2	11 Januari 2021	Bimbingan BAB 1, 2 dan 3	/
3	21 januari 2021	Bimbingan BAB 1, 2 dan 3 PPT	/
4	9 maret 2021	Bimbingan BAB 2	/
5	12 maret 2021	Bimbingan BAB 2	/
6	15 maret 2021	ACC Sempro	/
7	20 Mei 2021	Bimbingan setelah Sempro	/
8	7 Juni 2021	Bimbingan BAB 4	/
9	8 juni 2021	Bimbingan BAB 4	/
10	9 juni 2021	Bimbingan BAB 4	/
11	11 juni 2021	Bimbingan BAB 4	/
12	14 juni 2021	Bimbingan BAB 4	/
13	16 juni 2021	Bimbingan BAB 4	/
14	22 Juni 2021	Bimbingan BAB 4 dan 5	/
15	23 juni 2021	Bimbingan BAB 4 dan 5	/
16	2 Juli 2021	Bimbingan BAB 4 dan 5	/
17	2 Juli 2021	Bimbingan BAB 4 dan 5	/
18	21 Juli 2021	ACC Semhas	/
19	4 Agustus 2021	ACC Cetak	/

Ketua Program Studi  
Teknologi Laboratorium medis  
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## **Gambaran Disfungsi Tiroid Pada Penderita Diabetes Mellitus Tipe 2 (Studi Pustaka)**

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### **Abstrak**

Seorang penderita Diabetes Mellitus Tipe 2 yang memiliki kontrol glikemik yang buruk dapat menyebabkan disfungsi tiroid. Tujuan penelitian ini adalah mengkaji kadar T3, T4 dan TSH pada pasien Diabetes Mellitus Tipe 2. Jenis penelitian ini adalah studi kepustakaan menggunakan 10 artikel ilmiah yang terpublikasi secara nasional dan internasional. Hasil studi pustaka yang dilakukan pada 10 artikel ilmiah didapatkan hasil kadar T3, T4 dan TSH, kadar T3 terendah sampai tertinggi yaitu 0.0032 - 5.1 nmol/L, kadar T4 terendah sampai tertinggi yaitu 0.015 – 78.69 nmol/L dan kadar TSH terendah sampai tertinggi yaitu 0.38 – 20.26 mU/L. Kemudian ditemukan kelainan hipotiroid 11,9%, hipotiroid subklinis 18%, hipertiroid 1,37% dan hipertiroid subklinis 1,67% pada penderita DM tipe 2 dari 10 artikel ilmiah yang dikaji.

**Kata Kunci:** Disfungsi Tiroid pada penderita Diabetes Mellitus Tipe 2

## **Description Of Thyroid Dysfunction In Patients Diabetes Mellitus Type 2 (Literature Review)**

### *Abstract*

*A patient with Type 2 Diabetes Mellitus who has poor glycemic control can cause thyroid dysfunction. The purpose of this study was to examine the levels of T3, T4 and TSH in patients with Type 2 Diabetes Mellitus. This type of research was a literature study using 10 scientific articles published nationally and internationally. The results of a literature study conducted on 10 scientific articles showed that the levels of T3, T4 and TSH, the lowest to the highest T3 levels were 0.0032 - 5.1 nmol/L, the lowest to highest T4 levels were 0.015 - 78.69 nmol/L and the lowest to highest TSH levels were 0.38 – 20.26 mU/L. Then found 11.9% hypothyroidism, 18% subclinical hypothyroidism, 1.37% hyperthyroidism and 1.67% subclinical hyperthyroidism in patients with type 2 DM from 10 scientific articles studied.*

**Keywords:** *Thyroid dysfunction in patients with Type 2 Diabetes Mellitus*

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## Pendahuluan

Diabetes Mellitus Tipe 2 adalah kondisi Metabolik yang kompleks ditandai dengan peningkatan kadar glukosa darah akibat kerusakan kerja insulin (Sutanto, 2013). menurut *World Health Organization* (WHO) ada 422 juta orang dewasa yang menderita Diabetes Mellitus di seluruh dunia pada tahun 2019. Prevalensi pada orang dewasa meningkat dari 4,7% pada tahun 1980 menjadi 8,5% pada tahun 2019. Prevalensi penderita Diabetes Mellitus di Indonesia menempati urutan ke 4 dunia dengan jumlah penderita sebanyak 12 juta jiwa dan diperkirakan akan meningkat menjadi 21,3 juta jiwa pada tahun 2030, untuk di Provinsi Lampung pada tahun 2018 penderita Diabetes tertinggi berada di kota Metro dengan persentase 2,26%, kota Bandar Lampung 1,63%, Lampung Timur 1,14% dan Pringsewu 1,13% dari penduduk semua umur (Risksedas, 2018).

Disfungsi tiroid menunjukkan kelainan kelenjar tiroid yaitu kelebihan dan kekurangan hormon tiroid, disfungsi tiroid terdiri dari hipertiroid dan hipotiroid. Hipertiroid adalah keadaan dimana terjadi peningkatan hormon  $T_3$  dan  $T_4$  serta penurunan TSH, sedangkan hipotiroid adalah keadaan dimana terjadi penurunan hormon  $T_3$  dan  $T_4$  serta peningkatan TSH (Ghazali S.M dan Abbiyesku F.M, 2010).

Prevalensi disfungsi tiroid pada pasien Diabetes Mellitus Tipe 2 di laporkan sebesar 12,3% di Yunani dan 16% di arab saudi (Akbar, 2010). Diez dan Iglesias mempelajari 1.112 pasien dengan Diabetes Mellitus Tipe 2 (DMT2) dan 911 kontrol, dan menemukan bahwa 18,3% pasien dengan DMT2 mengalami hipotiroid, hipotiroid subklinis paling umum 6,9%, dibandingkan dengan 0,4% untuk hipotiroid nyata (British, 2018). Pada penelitian yang dilakukan (Wang, 2013) mengatakan hubungan diabetes mellitus tipe 2 dengan disfungsi tiroid terdapat pada kontrol glikemik. Kontrol glikemik yang ditandai dengan kadar Hemoglobin Adult 1c (HbA1c), kontrol glikemik yaitu cara tubuh untuk mempertahankan kadar glukosa dalam darah agar tetap normal. Seorang penderita diabetes mellitus tipe 2 dapat mengalami disfungsi tiroid ketika seorang

penderita diabetes mellitus tipe 2 memiliki kontrol glikemik yang buruk dan kontrol glikemik yang buruk dapat memperburuk kondisi diabetes mellitus tipe 2. Ketika seorang diabetes mellitus tipe 2 mengalami gangguan disfungsi sel-sel  $\beta$  dapat menyebabkan hiperglikemia dan insulin mengalami penurunan serta hormon lipase mengalami peningkatan disertai lipolisis yang meningkat dapat mempengaruhi FFA (Free Fatty Acid) dan hormon deodinase mengalami gangguan sehingga dapat menyebabkan disfungsi tiroid. Hiperglikemia dapat menyebabkan resistensi insulin (insulin dalam darah cukup tetapi tidak dapat berfungsi dengan baik atau terjadi kerusakan reseptor insulin) sehingga mengalami hiperinsulinemia dan terjadi proliferasi sel tiroid sehingga dapat menyebabkan disfungsi tiroid. Hormon leptin yang meningkat disebabkan oleh resistensi insulin dapat mempengaruhi hipotalamus sehingga TRH dan TSH mengalami gangguan dan menyebabkan disfungsi tiroid (Pandji, 2016).

Pada 19 artikel ilmiah terdapat 10 artikel ilmiah yang mengatakan adanya gangguan disfungsi tiroid pada penderita Diabetes Mellitus Tipe 2. Sebuah study menunjukkan disfungsi tiroid pada penderita Diabetes Mellitus Tipe 2 ditandai dengan kadar  $T_3$   $1.91\pm0.73$ ,  $T_4$   $78.69\pm20.69$  dan TSH  $20.26\pm22.60$  sebagian besar mengarah ke hipotiroid (Swamy et al 2015). Nilai normal  $T_3$  adalah 0,92-2,78 nmol/L, nilai normal  $T_4$  adalah 58-140 nmol/L dan nilai normal TSH adalah 0,5-4,7 mU/L (Joshi, 2011).

Berdasarkan uraian diatas maka penulis melakukan penelitian studi pustaka mengenai Gambaran Disfungsi Tiroid pada penderita Diabetes Mellitus Tipe 2.

## Metode

Jenis dan rancangan yang digunakan pada penelitian yang berjudul gambaran disfungsi tiroid pada penderita diabetes mellitus tipe 2 adalah studi kepustakaan (Library Research) yang didapat dengan menelaah artikel, jurnal ilmiah, dan buku yang berkaitan dengan disfungsi tiroid pada diabetes mellitus tipe 2 yang dipublikasikan secara nasional maupun internasional dalam waktu 10 tahun terakhir. Terdapat dua kriteria dalam penelitian ini yaitu kriteria inklusi yang mendukung penelitian yaitu jurnal yang memenuhi syarat yang

menjawab semua tujuan penelitian ini, sedangkan kriteria eksklusi adalah yang tidak mendukung penelitian ini yaitu jurnal yang hanya menjawab salah satu tujuan atau tidak menjawab semua tujuan penelitian ini. Waktu yang digunakan peneliti untuk melakukan penelitian kepustakaan ini yaitu dilaksanakan dari Maret-Juni 2021.

## **Hasil dan Pembahasan**

Hasil penelitian studi pustaka ini didapatkan dari kajian sepuluh artikel ilmiah yang dipublikasikan pada satu jurnal nasional dan sembilan jurnal internasional. Rentang tahun publikasi adalah tahun 2010 sampai 2020, kesepuluh artikel ilmiah yang dikaji meneliti kadar hormon tiroid dengan subjek penelitian adalah pasien diabetes mellitus tipe 2.

Tabel 4.2 Kadar T3, T4, dan TSH pada penderita Diabetes Mellitus Tipe 2 yang mengalami Disfungsi Tiroid

No	Penulis	Subjek	T3 (nmol/ L)	T4 (nmol/ L)	TSH (mU/ L)	Kesimpulan Hipertiroid/ Hipotiroid
1.	Ghazali et al, (2010)	64 pasien diabetes tipe 2 dan 36 kontrol non diabetes dengan usia yang sama	0.0032 ± 0.0059	0.0106 ± 0.021	0.38 ± 4.32	Dari 64 pasien DM tipe 2 didapatkan 19 (29,7%) yang mengalami disfungsi tiroid. (15,8%) hipotiroid subklinis dan (5,2%) hipertiroid subklinis.
2.	Mardia ntoet al, (2010)	40 subjek diabetes mellitus tipe 2	-	1.45± 0.55	3.97± 4.48	Dari 40 pasien DM tipe 2 didapatkan 4 (10%) yang mengalami gangguan tiroid. 2 (5%) mengalami hipotiroid subklinik dan 2 (5%) mengalami hipertiroid subklinis.
3.	Uppal et al, (2012)	120 subjek penderita diabetes mellitus tipe 2	0.01±0.00	6.84± 3.16	10.81 ±6.25	Dari 120 pasien DM tipe 2 didapatkan (24,5%) mengalami kelainan tiroid. 20 (17%) penderita hipotiroid dan 9 (7,5%) penderita hipertiroid.
4.	Geffari et al, (2013)	411 pasien diabetes tipe 2	0.0046 ±0.0014	0.0159 ± 0.0035	3.4± 2.9	Dari 411 pasien DM tipe 2 (44,3%) mengalami disfungsi tiroid berupa: hipotiroid (25,3%), hipotiroid subklinis (15,3%), hipertiroid (3,2%) dan hipertiroid subklinis (0,5%).
5.	Manjun at et al, (2013)	100 pasien diabetes tipe 2 (50 pasien pria dan 50 wanita)	0.04±0.01	1.58±0.18	8.15± 0.57	Dari 100 pasien DM tipe 2 (84,6%) mengalami hipotiroid subklinis.
6.	Swamy et al, (2015)	58 pasien diabetes mellitus tipe 2	1.91 ± 0.73	78.69± 20.69	20.26 ± 22.60	Dari 58 pasien DM tipe 2 (43,09%) mengalami disfungsi tiroid yaitu (12,06%) mengalami hipotiroid dan (31,03%) mengalami hipotiroid subklinis.
7.	Yeqing et al, (2017)	15.269 pasien diabetes mellitus tipe 2	0.0055 ± 0.168	0.005± 0.0157	1.9± 2.3	Dari 15.269 pasien DM tipe 2 didapatkan (16,2%) pada laki-laki dan 7,7% pada perempuan yang mengalami hipotiroid.
8.	Elgazar et al, (2019)	200 pasien dengan diabetes tipe 2 dan 200 kontrol	0.46 ± 0.00	1.39± 0.03	2.94± 1.8	Dari 200 pasien DM tipe 2 (29%) mengalami disfungsi tiroid berupa: hipotiroid nyata (7%), hipotiroid subklinis (13%), hipertiroid nyata (3%) dan hipertiroid subklinis (6%).

9.	Talwal kar Et al, (2019)	Sebanyak 1.508 pasien. Diabetes mellitus tipe 2 sebanyak 504, hipertensi 501 pasien, diabetes mellitus tipe 2 dan hipertensi 503 pasien	0.06±0. 16	0.14± 0.88	3.3± 7.04	Dari 1.508 pasien DM tipe 2 didapatkan (26,9%) yang mengalami hipotiroid.
10.	Sami et al, (2020)	251 pasien diabetes tipe 2	5.1± 1.32	13.02± 3.02	2.89± 2.56	Dari 251 pasien DM tipe 2 didapatkan (14,8%) yang mengalami penyakit tiroid.

Catatan: kadar T3,T4 sudah diconvert ke satuan nmol/L dan kadar TSH sudah diconvert ke satuan mU/L

Pemeriksaan skrining T3, T4 dan TSH pada penderita diabetes mellitus tipe 2 (DM tipe 2) sangat penting sebagai langkah awal deteksi dini untuk melihat ada atau tidak disfungsi tiroid pada penderita DM tipe 2. Tabel 4.1 menunjukkan hasil dari 10 artikel ilmiah dan ditemukan adanya disfungsi tiroid pada penderita DM tipe 2 sebagai subjek penelitian. Nilai Normal T3 0,92-2,78 nmol/L, nilai normal T4 58-140 nmol/L dan nilai normal TSH 0,5-4,7 mU/L. Setelah mengkaji dari 10 artikel ilmiah didapatkan kadar T3 terendah-tertinggi yaitu 0.0032-5.1 nmol/L, kadar T4 terendah-tertinggi yaitu 0.015-78.69 nmol/L, kadar TSH terendah-tertinggi 0.38-20.26 mU/L. Pada 10 artikel ilmiah didapatkan rata-rata sebesar 35,6% penderita DM tipe 2 mengalami disfungsi tiroid diantaranya 11,9% mengalami hipotiroid, 18 % mengalami hipotiroid subklinis, 1,37% mengalami hipertiroid dan 1,67% mengalami hipertiroid subklinis. Secara teori DM tipe 2 dan disfungsi tiroid saling mempengaruhi satu sama lain. Ketika penderita DM tipe 2 mengalami disfungsi tiroid, maka kondisi ini akan memperburuk penyakit DM tipe 2 yang diderita (Uppal, 2013). Penderita DM tipe 2 yang mengalami disfungsi tiroid dapat melakukan pemeriksaan HbA1c (Hemoglobin A1c) hal ini dilakukan untuk pemantauan pengobatan dan diet, rata-rata jumlah hemoglobin A1c berikatan dengan glukosa secara tiga bulan terakhir hal ini dapat memastikan kontrol glikemik (Pandji, 2016).

Disfungsi tiroid lebih banyak ditemukan pada penderita DM tipe 2 dari pada penderita DM tipe 1, ketika penderita DM tipe 2 mengalami gangguan kontrol glikemik dapat menyebabkan disfungsi tiroid. DM tipe 1 merupakan penyakit autoimun yaitu kondisi sistem kekebalan tubuh berbalik menyerang sel tubuh yang sehat sehingga pada penderita DM tipe 1 mengalami kekurangan insulin (Uppal, 2013).

Pada pasien DM tipe 2 umumnya terjadi 3 jenis kondisi yaitu resistensi insulin, hiperglikemia akibat kontrol glikemik yang buruk dan disfungsi sel-sel  $\beta$  pankreas. Ketiga kondisi ini dapat mempengaruhi satu sama lain. Ketika sel-sel  $\beta$  pankreas mengalami kerusakan maka hormon insulin akan mengalami penurunan dan mengakibatkan adanya kenaikan hormon lipase sehingga lipolisis meningkat. Hal ini menyebabkan FFA (free fatty acid) mengalami peningkatan sehingga enzim deiodinase yang berfungsi membantu konversi T4 ke T3 mengalami penurunan dan berakibat langsung terhadap hormon T4 dan T3.

Disisi lain disfungsi Sel-sel  $\beta$  pankreas dapat menyebabkan hiperglikemia begitu pula sebaliknya. Ketika pasien DM tipe 2 mengalami hiperglikemia hal ini dapat meningkatkan sistesis glikogen secara maksimal agar glukosa dalam darah tidak tinggi dan tersimpan di otot atau hati. Dampak buruk dari peningkatan sintesis glikogen adalah kenaikan FFA yang secara tidak langsung mengganggu proses konversi T4.

Resistensi insulin dapat menyebabkan hiperglikemia dan juga sebaliknya. Pada resistensi insulin terjadi hiperinsulinemia yang menyebabkan terganggunya proliferasi sel tiroid. Hal ini mengakibatkan terganggunya produksi hormon tiroid sehingga terjadi disfungsi tiroid. Disamping itu resistensi insulin meningkatkan hormon leptin yang berfungsi mengendalikan nafsu makan serta rasa lapar. Peningkatan hormon leptin dapat memperngaruhi hipotalamus sehingga ketika hipotalamus terganggu, maka TRH dan TSH juga mengalami gangguan dan mengakibatkan disfungsi tiroid (Pandji, 2016).

### Kesimpulan

Berdasarkan hasil dan pembahasan studi pustaka yang telah dilakukan terhadap 10 artikel ilmiah, dapat disimpulkan bahwa pada 10 artikel ilmiah tersebut didapatkan hasil kadar T3, T4 dan TSH yaitu:

1. Kadar T3 terendah sampai tertinggi yaitu 0.0032 - 5.1 nmol/L pada penderita DM tipe 2 dari 10 artikel ilmiah yang dikaji.
2. Kadar T4 terendah sampai tertinggi yaitu 0.015 - 78.69 nmol/L pada penderita DM tipe 2 dari 10 artikel ilmiah yang dikaji.
3. Kadar TSH terendah sampai tertinggi yaitu 0.38 - 20.26 mU/L pada penderita DM tipe 2 dari 10 artikel ilmiah yang dikaji.

### Saran

1. Penelitian selanjutnya diharapkan dapat melihat korelasi HbA1c dengan disfungsi tiroid.
2. Penelitian selanjutnya disarankan untuk melihat kadar T3, T4 dan TSH pada pasien DM tipe 1.

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