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# Association of Type 2 Diabetes Mellitus and Thyroid Disease: The Systematic Review and Meta Analysis

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## Abstract

**Introduction:** Patients with Type 2 Diabetes Mellitus (T2DM) are more susceptible to thyroid disorders. Many diabetic patients exhibit features of thyroid dysfunction over a period of time. This study was designed to collect data on the association between T2DM and thyroid disease.

**Materials and methods:** This study is a systematic review and meta-analysis. Source of this study data comes from literature obtained through the internet in the form of research results published on the internet, both in Cochrane, PubMed, Googlescholar, and other journal databases. We searched for the keywords “blood glucose” and “thyroid disease”. The inclusion criteria of the research that will be included are studies that examine the relationship between thyroid disease and blood glucose levels, with adult research subjects (not animal studies), research conducted within the last ten years and using primary data.

**Results:** We found several relevant journals or articles related to the relationship between thyroid disease and blood glucose levels. The search results in the Pubmed journal database, we found four journal that discusses the relationship between thyroid disease and blood glucose levels. A Google scholar search shows two studies relevant to this study.

**Conclusion:** The findings of this systematic review showed that mircroRNA functions as a tumor suppressor or a promoter in cholangiocarcinoma.

## Keywords

Blood glucose; Hyperthyroidsm; Hypothyroidsm; Thyroid disease; Type 2 Diabetes Mellitus

## Abbreviations

T2DM: Type 2 Diabetes Mellitus; DM: Diabetes Mellitus; WHO: World Health Organization; TD: Thyroid Disease; T1DM: Type 1 Diabetes Mellitus; FPG: Fasting Plasma Glucose; TRH: Thyrotropin Releasing Hormone; GO: Graves’s Orbitopathy; PEPCK: Phosphoenolpyruvate Carboxykinase;

## Introduction

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from impaired insulin secretion, insulin action, or both [1]. The World Health Organization (WHO) estimates that the global prevalence of T2DM will increase from 171 million people in 2000 to 366 million in 2030. World Health Organization estimates that Indonesia is ranked 4th in the world in terms of the number of DM sufferers after China, India and United States of America [2,3]. The number of people with diabetes in Indonesia in 2000 reached 8.4 million and is estimated to be 21.3 million by 2030, but only 50% of them are aware that they have DM, and only 30% of sufferers have regular check- ups [2,3].

Patients with Type 2 Diabetes Mellitus (T2DM) are more susceptible to thyroid disorders. Many diabetic patients exhibit features of thyroid dysfunction over a period of time [4,5]. Insulin resistance plays an important role in the development of hypothyroidism in patients with type 2 diabetes mellitus.

Insulin resistance has been the most important aspect linking thyroid dysfunction and T2DM. Insulin resistance is a condition that occurs in both hypothyroidism and hyperthyroidism. This can be done by primary care physicians involved in treating diabetic patients. Early treatment of thyroid dysfunction in diabetic patients will help normalize their glycemic status and lipid profile [6,7].

According to a huge European meta-examination, Thyroid Disease (TD) is available in 3.82% of everybody [8]. Its predominance among those with T2DM is fundamentally higher, going from 9.9 to 48% [9]. This wide scope of predominance can be clarified by the utilization of various definitions for TD finding, contingent upon the presence of hostile to thyroid peroxidase (against TPO), antithyroglobulin counter acting agent (against TG), or both [10].

In many investigations, most T2DM patients with TD had subclinical hypothyroidism and a few new instances were analyzed during clinical assessments, featuring the requirement for upgraded evaluating for TD in T2DM patients. Thyroid disease is more normal in T1DM than in T2DM patients, yet the pathophysiology is more complicated in T2DM patients and has more noteworthy clinical ramifications [10]. This study was designed to collect data on the association between T2DM and thyroid disease.

## Materials and Methods

This study is a systematic review and meta-analysis. Source of this study data comes from literature obtained through the internet in the form of research results published on the internet, both in Cochrane, PubMed, Googlescholar, and other journal databases. We searched for the keywords “blood glucose” and “thyroid disease”. The research included in this is research that focuses on the relationship between thyroid disease and blood glucose levels. The inclusion criteria of the research that will be included are studies that examine the relationship between thyroid disease and blood glucose levels, with adult research subjects (not animal studies), research conducted within the last ten years and using primary data. The purpose of this study was to examine the relationship between thyroid disease and blood glucose levels.

## Results

We found several relevant journals or articles related to the relationship between thyroid disease and blood glucose levels. The search results in the Pubmed journal database, we found four journal that discusses the relationship between thyroid disease and blood glucose levels. A Google scholar search shows two studies relevant to this study. Information on all the studies involved in this systematic review can be seen in **Table 1**.

| Author | Origin | Method | Sample Size | Population | Period | Level | Outcome |
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| | | Cross | | Patients with type 2 diabetes mellitus attending the out-patient department | From June | Overt hypothyroidism: TSH value above 10 mU/L and low free T3& T4 levels. Sub-clinical hyperthyroidism: TSH with | The prevalence of thyroid dysfunction is 17.5% in patients |

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| Mehalingam, et al. (2020) | India | sectional study | 331 sample | without any prior history of thyroid disease, chronic liver disease or acute illness were recruited for the study. | 2016 to 01-05-2019 | normal free T3& T4 levels. Overt hyperthyroidism: low TSH with high free T4 levels. Dyslipidemia: total serum cholesterol was above 200 mg/dL. | with type 2 diabetes mellitus. Thyroid dysfunction did not have any correlation with diabetic complications. |
| Ozair, et al (2018) | India | Cross sectional study | 250 sample | Type 2 DM patients were enrolled aged between 40 and 75 years. | 2017 | Overt hypothyroidism: TSH value above 10 mU/L and low free T3& T4 levels. Sub-clinical hyperthyroidism: TSH with normal free T3& T4 levels. Overt hyperthyroidism: low TSH with high free T4 levels. Poor glycemic state: HbA1c ≥7 | A high prevalence of thyroid dysfunction (28%) was observed in type 2 diabetic patients with subclinical hypothyroidism (18.8%) as the commonest thyroid disorder. Thyroid dysfunction was more prevalent in females, with presence of dyslipidemia, retinopathy, poor glycemic state (HbA1c ≥7) and longer duration of diabetes as significant contributing factors associated. |
| Elgazar, et al. (2019) | Egypt | Cross sectional study | 200 patients and 200 control | Patients diagnosed to have type 2 DM with age ranging from 30 to 65 years were included in the study group. | From November 2017 to November 2018 | Overt hypothyroidism: TSH value above 10 mU/L and low free T3& T4 levels. Sub-clinical hyperthyroidism: TSH with normal free T3& T4 levels. Overt hyperthyroidism: low TSH with high free T4 levels. Poor glycemic state: HbA1c ≥8 | There was a significant increase in serum TSH and T3 levels in diabetics when compared with the controls, (Pâ?¯<â?¯0.001, Pâ?¯=â?¯0.001), respectively. Thyroid dysfunction was significantly more prevalent in patients with HbA1câ?¯≥â?¯8%,(Pâ?¯=â?¯0.0001), and in those having longer diabetes duration, (Pâ?¯<â?¯0.001) |
| | | | | | | | The results show that 43.5% and37.3% of T2DM and control |

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| Ogbonna, et al. (2019) | Nigeria | Retrospective study | 354 patients | All patients with T2DM irrespective of blood pressure status, 40 years of age at the time of diagnosis of DM20, no thyroid surgery nor trauma to the neck. | No data | Overt hypothyroidism: TSH value above 10 mU/L and low free T3& T4 levels. Sub-clinical hyperthyroidism: TSH with normal free T3& T4 levels. Overt hyperthyroidism: low TSH with high free T4 levels. | subjects, respectively, were males. Mean HbA1c was significantly higher in T2DM patients than in the controls (7.8 ± 2.0% vs. 5.8 ± 1.2%, p=0.001), while mean fT3 was significantly lower in T2DM patients than in the controls (2.3 ± 1.5 pg/mL vs. 2.7 ± 2.2 pg/mL, p=0.03). Mean HbA1c was significantly higher in T2DM patients with thyroid dysfunction compared to their euthyroid counterparts (8.1 ± 1.9% vs. 5.1 ± 1.2%, p=0.001). HbA1c had a positive linear relationship with the presence of thyroid dysfunction (regression coefficient=1.89, p=0.001) |
| Chen, et al(2014) | Taiwan | Retrospective study | 4.195 GD patients and 16.78 non-GD patients | Patients with newly diagnosed Graves' disease (GD) | From January 1998 to December 2008 were identified | Does not mention thyroid and blood sugar levels, but directly provides a patient diagnosis based on medical records | The GD patients were more likely to have diabetes (8.03% vs. 4.48%, P < 0.0001), hypertension (18.1% vs. 13.5%, P < 0.0001), hyperlipidemia (11.9% vs. 9.09%, P < 0.0001) and coronary artery disease (10.3% vs. 5.86%, P < 0.0001) than the control patients were. |
| Talwalkar, et al (2018) | India | Cross sectional study | 1508 patients | Adult patients with T2DM and/or hypertensio (who were already receiving antidiabetic/anti hypertensive therapies) | June to September 2017 | Fasting plasma glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% | The proportion of obese against overweight hypothyroid patients was higher in all indications (T2DM: 16.5% vs 3.4%; hypertension A considerable proportion of patients with SCH was prescribed thyroxine in T2DM (61.5%), 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 |

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| | | | | | | | hypothyroidism and SCH cases, respectively, in all cohorts |

# Discussion

The insulin resistance normally found in patients with Type 2 Diabetes Mellitus assumes a significant part in the improvement of thyroid brokenness in these patients. Thyroid brokenness can happen as hypothyroidism and hyperthyroidism. Subclinical hypothyroidism can likewise happen in diabetic patients and can prompt intricacies of diabetes like retinopathy, neuropathy, and cardiovascular infection [7].

A study conducted by Ogbonna showed that HbA1c had a positive linear relationship with thyroid dysfunction (hypothyroidism or hyperthyroidism) with regression coefficient of 1.89 (p=0.001) [11,12]. The regression equation is as follows: HbA1c=4.17+1.89 (class of thyroid function). This suggests that poor glycemic control is directly linked to the development of thyroid dysfunction in T2DM [12].

This may be as a result of the effect of hyperglycemia on hypothalamo-pituitary-thyroid axis that ultimately leads to low T3 levels in patients with DM. It may also be due to the hyperglycemia-induced inhibition of peripheral deiodination of T4 to T3, causing a low T3 state [12].

The obsessive components of T2DM incorporate expanded digestive glucose take-up, diminished insulin discharge, and changes in cell mass with indications related with expanded insulin debasement, expanded glucagon emission, expanded hepatic glucose creation, expanded catecholamines, and insulin resistance [7]. These elements have been examined to be a basic piece of hyperthyroidism. In this way, a neurotic benchmark convergence happens which gives us pieces of information about the different physiological abnormalities normal to hyperthyroidism and T2DM [13-16].

Among the above-mentioned symptomatology, insulin resistance has been the most important aspect linking thyroid dysfunction and T2DM. Insulin resistance is a condition that occurs in both hypothyroidism and hyperthyroidism. Insulin resistance in muscle and liver is a hallmark of T2DM. Undisturbed glucose homeostasis and an intact insulin secretory response and undisturbed tissue sensitivity to insulin are essential for maintaining normal blood glucose levels [15,16].

Glucose clearance is mediated by the combined effects of insulin and hyperglycemia to modulate three basic phenomena, first, decreased endogenous (hepatic) glucose production, second increased glucose absorption (liver and splanchnic), third, glucose upregulation by peripheral tissues (skeletal muscle). Uptake of glucose into muscle is modulated by glycolysis and glycogen synthesis [15,16].

Hepatic insulin resistance is described by overabundance glucose creation regardless of fasting hyperinsulinemia, and expanded hepatic glucose yield rate is a significant modulator of expanded Fasting Plasma Glucose (FPG) fixation in T2DM subjects. In insulin obstruction in the post-absorptive state, muscle glucose is upregulated yet ingestion proficiency is decreased. Under such conditions, diminished glucose take-up into muscle and expanded hepatic glucose yield lead to deteriorating of glucose digestion [15,16].

The term symphonious group of four is utilized to address the center pathology of insulin opposition. Liberation of glucose removal and digestion in adipocytes, muscle, and liver, along with impeded insulin emission by pancreatic beta cells, comprise the four significant organ framework issues that assume an authoritative part in the pathogenesis of T2DM. It ought to be considered that insulin obstruction has turned into a demonstrated condition in hyperthyroidism just as hypothyroidism [15,16]

Insulin resistance likewise causes lipid digestion problems as indicated by ongoing discoveries. Consequently, apparently insulin obstruction is a potential connection among T2DM and thyroid brokenness. Insulin opposition and cell work are

contrarily associated with thyroid-invigorating chemical which can be clarified by the insulin enemy impact of thyroid chemical alongside an expansion in TSH [15,16].

A higher serum TSH normally compares to a lower thyroid chemical through a negative input system. At the point when TSH expands, thyroid chemical abatements and the opposing impact of insulin debilitates. These perceptions recommend that insulin irregularity is firmly identified with thyroid brokenness and a wonder interceded through cell brokenness [15].

Diabetes influences thyroid capacity by changing the TSH level and disabling the transformation of T4 to T3 in the fringe tissues. In euthyroid DM patients, the nighttime TSH top is missing or decreased and the TSH reaction to Thyrotropin Releasing Hormone (TRH) is additionally disabled. Hyperglycaemia of longer length can cumulatively affect TD [10].

While deciphering thyroid capacity tests, think about that, as other intense fundamental sicknesses, diabetic ketoacidosis can diminish T3 and T4 levels while TSH levels stay typical. Insulin opposition and hyperinsulinaemia lead to multiplication of thyroid tissues, an expanded occurrence of nodular thyroid illness, and a bigger goiter [10].

In hypothyroid patients with existing together diabetes, the adequacy of thyroid chemical treatment might be influenced. T1DM is more normal in patients with Graves's Orbitopathy (GO) than in the typical populace; GO is more regular and extreme in Graves' infection patients with T2DM and is fundamentally connected with term, stoutness, and vasculopathy. Diabetic patients with GO likewise have a higher occurrence of dysthyroid optic neuropathy than nondiabetics [10].

**Type 2 DM and Hyperthyroid**

Hyperthyroidism and thyrotoxicosis can deteriorate subclinical DM and cause hyperglycaemia in T2DM patients, expanding the danger of diabetic entanglements. T2DM decreases thyroid-animating chemical levels and weakens the change of thyroxine (T4) to triiodothyronine (T3) in the fringe tissues. Inadequately oversaw T2DM can prompt insulin opposition and hyperinsulinaemia, which causes thyroid tissue multiplication and expands knob arrangement and goitre siz [10].

Abundance flowing thyroid chemicals in hyperthyroidism is related with poor glycaemic control, including hyperglycaemia and insulinopenia. At the point when typical people foster hyperthyroidism, almost 2-3% of them foster unmistakable diabetes. Almost half of those with Graves' illness have some level of glucose prejudice. Diabetic patients with hyperthyroidism experience deteriorated glycaemic control. Thyrotoxicosis can hasten diabetic intricacies, for example, diabetic ketoacidosis and endothelial brokenness, who expands the danger of cardiovascular comorbidities [13,17,18].

Thyroid chemical can follow up on different organs to influence glucose digestion. It increments gastrointestinal motility and improves glucose assimilation. In the liver, it expands the movement of Phosphoenolpyruvate Carboxykinase (PEPCK), a protein that upgrades gluconeogenesis. This hepatic gluconeogenesis may happen through the immediate impact of the thyroid chemical or by implication by means of glucagon or catecholamine [17,18].

The improved glycogenolysis and expanded hepatic glucose yield incites hyperinsulinaemia and glucose prejudice, causing fringe insulin opposition. This demolishes subclinical diabetes and misrepresents the hyperglycaemia in T2DM, expanding the danger of diabetic intricacies. In the fat tissues, thyroid chemical increments lipolysis, the expanded serum free unsaturated fat level causes insulin obstruction. Raised lipolysis and expanded hepatic β-oxidation, confounded by an insulin-inadequate state, can prompt ketoacidosis [17,18].

Hyperthyroidism expands GLUT4 quality articulation and glucose take-up in skeletal muscles. Thyroid chemicals additionally straightforwardly control insulin discharge by beta cells. Hypothyroidism decreases glucose-instigated insulin discharge, while hyperthyroidism upgrades the reaction of beta cells to glucose. Debasement of insulin is additionally expanded by thyroid chemical, and thyrotoxicosis builds insulin freedom. Thyroid chemical additionally expands glucagon discharge by

pancreatic alpha cells [17,18].

**Type 2 DM and Hypothyroid**

Diabetes have shown a significant association with hypothyroidism [17-20]. We undertook this study to determine the prevalence of hypothyroidism in patients with T2DM and further explored the management strategies [14]. Hypothyroidism was more normal among the subjects of the examination directed by Mehalingam [6]. Another investigation showed that the pervasiveness of subclinical hypothyroidism in diabetic patients was 18.8%.

They examination likewise tracked down that the pervasiveness of thyroid brokenness was higher among ladies, patients with dyslipidemia and retinopathy and patients with poor glycemic control and long length of diabetes [11]. The discoveries of this investigation are in accordance with this examination which didn't show a connection between's thyroid brokenness and diabetes entanglements in the examination subjects [6].

However, one more examination led in Egypt showed that the predominance of thyroid brokenness expanded with an increment in glycosylated hemoglobin demonstrating that poor glycemic control might assume a part in event of thyroid brokenness in diabetic patients. Aside from insulin obstruction, autoimmunity additionally assumes a part in the advancement of thyroid brokenness in patients with Type 2 Diabetes Mellitus [19].

An investigation led by Radaideh AR et al. showed that 12.5% of diabetic patients were found to have thyroid illness [20]. Among diabetic patients with thyroid brokenness, thyroid peroxidase counter acting agent was observed to be positive in 8.3% of cases. This examination recommends that evaluating for asymptomatic thyroid brokenness can be useful in diagnosing thyroid sickness among diabetic patients [6,20]

Thyroid hormones play an important role in maintaining regular blood glucose, circulating levels of insulin, and counter regulatory hormone like epinephrine. In patients with poorly controlled diabetes, reduced T3 levels have been observed along with impairment of the response of serum TSH to thyrotropin releasing hormone stimulation. Hyperinsulinemia in association with insulin resistance has shown a proliferative effect on thyroid tissue resulting in increased formation of thyroid nodules [14].

# Conclusion

Blood sugar levels in diabetic and thyroid patients are related to each other, both for hyperthyroidism and hypothyroidism.

# References


1. Kasper LD, Fauci AS, Hauser SL, et al. Harrison’s principles of internal medicine 19th edition. New York: McGraw-Hill Education. 2018.
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018; 14(2):88-98.
3. Kementerian Kesehatan Republik Indonesia. Riset Kesehatan Dasar. 2018.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diab Care. 2016; 62-69.
5. Demitrost L, Ranabir S. Thyroid dysfunction in type 2 diabetes mellitus: A retrospective study. Indian J Endocrinol Metab. 2012;16: 334-335.
6. Mehalingam V, Sahoo J, Bobby Z, et al. Thyroid dysfunction in patients with type 2 diabetes mellitus and its association with diabetic complications. J Fam Med Prim Care. 2020; 9(8):4277-4281.
7. Wang C. The relationship between type 2 diabetes mellitus and related thyroid diseases. J Diabetes Res. 2013; 1-9.
8. Garmendia MA, Santos PS, Guillén-Grima F, et al. The incidence and prevalence of thyroid dysfunction in Europe: A meta-analysis. J Clin Endocrinol Metab. 2014; 99:923-931.
9. Centeno MM, Gomez RL, Fregenal M, et al. Prevalence of thyroid dysfunction in patients with type 2 diabetes

mellitus. Medicina (B Aires). 2016; 76:355-358.

10. Kalra S, Aggarwal S, Khandelwal D. Thyroid dysfunction and type 2 diabetes mellitus: screening strategies and implications for management. Diabetes Ther. 2019; 10(6):2035-2044.
11. Ozair M, Noor S, Raghav A, et al. Prevalence of thyroid disorders in north Indian type 2 diabetic subjects: A cross sectional study. Diabetes Metab Syndr. 2018; 12:301–304.
12. Ogbonna SU, Ezeani IU, Okafor CI, et al. Association between glycemic status and thyroid dysfunction in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2019; 12:1113-1122.
13. Chen HH, Yeh SY, Lin CL, et al. Increased depression, diabetes and diabetic complications in Graves' disease patients in Asia. QJM. 2014; 107(9):727-733.
14. Talwalkar P, Deshmukh V, Bhole M. Prevalence of hypothyroidism in patients with type 2 diabetes mellitus and hypertension in India: a cross- sectional observational study. Dovepress. 2018; 12:369-376.
15. Chen G, Wu J, Lin Y, et al. Associations between cardiovascular risk, insulin resistance?-cell function and thyroid dysfunction: a cross-sectional study in She ethnic minority group of Fujian Province in China. Eur J Endocrinol. 2010; 163(5):775-782.
16. Kapadia KB, Bhatt PA, Shah JS. Association between altered thyroid state and insulin resistance. J Pharmacol Pharmacother. 2012;3:-156-160.
17. Nishi M. Diabetes mellitus and thyroid diseases. Diabetol Int. 2018; 9(2):108-112.
18. Ray S, Ghosh S. Thyroid disorders and diabetes mellitus: double trouble. J Diabetes Res Ther. 2016; 2:1-7.
19. Elgazar EH, Esheba NE, Shalaby SA, et al. Thyroid dysfunction prevalence and relation to glycemic control in patients with type 2 diabetes mellitus. Diabetes Metab Syndr. 2019; 13:2513-2517.
20. Radaideh AR, Nusier MK, Amari FL, et al. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. Saudi Med J. 2004; 25:1046-1050.