Thyroid Dysfunction and Its Association with Glycemic Control in Patients with Type 2 Diabetes Mellitus (T2DM): A Systematic Review and Meta-Analysis

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ABSTRACT

Background: *Diabetes mellitus (DM) is characterized by metabolic anomalies, such as hyperglycemia, resulting from pancreatic β cell dysfunction. In this context, thyroid dysfunction is the second most prevalent endocrine disorder after DM, and the interaction with glycemic control in type 2 diabetes mellitus (T2DM) remains a topic of debate. Therefore, this meta-analysis aimed to evaluate the impact of thyroid dysfunction on glycemic control in T2DM patients.* ***Methods:*** *A systematic literature search was conducted using ScienceDirect, the Cochrane Library, and PubMed up to December 8, 2024, under PRISMA guidelines. Research evaluating the effect of thyroid dysfunction on glycemic control in T2DM was included, with Glycated hemoglobin (HbA1c) levels as the primary outcome measure. Furthermore, research lacking relevant outcome data, full-text availability, or appropriate design was excluded. Data extraction and quality assessment were performed collaboratively, using the STROBE checklist. Meta-analysis was conducted using Review Manager 5.4, with mean difference (MD) and 95% confidence intervals (CI) as the effect size. Random-effects models were used to account for anticipated clinical heterogeneity, assessed by Higgins' I-squared (I^2) statistic.* ***Results:*** *The initial search identified 1,397 research studies, with only 3 papers meeting the inclusion criteria. A pooled analysis reported a significant increase in HbA1c levels in T2DM patients with thyroid dysfunction (MD: 1.94, 95% CI: 0.73 - 3.14; $p < 0.000001$) with high heterogeneity ($I^2 = 98\%$).* ***Conclusion:*** *Thyroid dysfunction was prevalent in T2DM patients and was associated with poorer glycemic control. Routine thyroid function assessment could also be integrated into T2DM management to optimize metabolic outcomes.*

Keywords: *Type 2 Diabetes Mellitus, Thyroid Dysfunction, Glycemic Control, Endocrine Disorder.*

INTRODUCTION

The hallmark of metabolic anomalies in diabetes mellitus (DM) is hyperglycemia caused by pancreatic β-cell malfunction.[1,2] Thyroid dysfunction is the second most prevalent endocrine disorder after DM.[3-6] There are several methods used for the interaction of the two conditions. Furthermore, the pathophysiology of hyperthyroidism is significantly influenced by the anomalies associated with insulin resistance, such as increased glucagon secretion, hepatic glucose synthesis, insulin breakdown, and catecholamines.[7]

People with type 2 diabetes mellitus (T2DM) have a high frequency of thyroid dysfunction. Some research showed that the incidence of thyroid dysfunction was not significantly different from the general population.[8,9,10] Among several

physiological effects, thyroid hormones can have an impact on glucose metabolism. These include lipolysis, intestinal glucose absorption, and overall metabolic stimulation. Insulin resistance and hyperglycemia are also induced in healthy volunteers when thyroid hormone is administered. Meanwhile, oxyhyperglycemia and insulin resistance are observed in thyrotoxicosis patients.[11] Diabetes causes hyperthyroidism, which can be mistaken for T2DM when ignored. Obesity results from hypothyroidism due to a decreased overall metabolic rate, which produces insulin resistance and glucose intolerance.[11]

Thyroid dysfunction is among the most prevalent medical conditions. The Japan Thyroid Association estimates that between 5 and 7 million people suffer from thyroid disease. This includes thyroid nodules, which account for 4 to 5.5% of the total population. According to the 2018 National Health and Nutrition Examination Survey, the estimated prevalence of diabetes in Japan is 9.3% and 18.7% for females and males, respectively.[12] Many people have both diabetes and thyroid dysfunction since the two conditions are common. People with diabetes have a disproportionately greater frequency of thyroid dysfunction compared to the general population.[13] This meta-analysis evaluates the effect of thyroid dysfunction on glycemic control in T2DM.

METHODS

This meta-analysis was conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria. The Protocol of the research containing details of the literature search strategy has been registered and published in PROSPERO with the registration number CRD42024628903. Using ScienceDirect, the Cochrane Library, and PubMed, a comprehensive search of the literature was conducted up to December 8th, 2024. "(("thyroid gland"[MeSH Terms] OR ("thyroid"[All Fields] AND "gland"[All Fields]) OR "thyroid gland"[All Fields] OR "thyroid"[All Fields] OR "thyroid usp"[MeSH Terms] OR ("thyroid"[All Fields] AND "usp"[All Fields]) OR "thyroid usp"[All Fields] OR "thyroids"[All Fields] OR "thyroid s"[All Fields] OR "thyroidal"[All Fields] OR "thyroideal"[All Fields] OR "thyroidism"[All Fields] OR "thyroiditis"[MeSH Terms] OR "thyroiditis"[All Fields] OR "thyroiditides"[All Fields]) AND ("glycemic control"[MeSH Terms] OR ("glycemic"[All Fields] AND "control"[All Fields]) OR "glycemic control"[All Fields])) AND (observationalstudy[Filter])" were the keywords predefined for the literature search. Articles with relevant titles and abstracts were evaluated in full and subjected to additional analysis.

Inclusion and Exclusion Criteria

Research was screened according to the inclusion criteria as follows: 1) analysis of the effect of thyroid dysfunction on glycemic control in T2DM with extractable outcomes, and 2) the primary outcome is HbA1c levels in T2DM patients with normal and abnormal thyroid. Meanwhile, exclusion criteria included 1) irretrievable full-text articles, and 2) inappropriate research design, intervention, or outcome. Figure 1 shows details of the research search strategy.

Data Extraction and Risk of Bias Assessment

Data were extracted from the selected articles and assessed in terms of quality by using STROBE. Quality assessment was achieved collaboratively by all reviewers until a consensus was reached.

Statistical Analysis

Meta-analysis was performed with Review Manager ver 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). Furthermore, Mean Difference (MD) with 95% confidence interval (CI) was selected as the common measure. Effect sizes were pooled using random-effects models after anticipating clinical heterogeneity. The analysis result was considered significant when p-value<0,005. Heterogeneity was investigated using the Higgins I-squared (I^2) statistical model, and the test results were classified as negligible (0-25%), low (25%-50%), moderate (50-75%), or high (<75%).

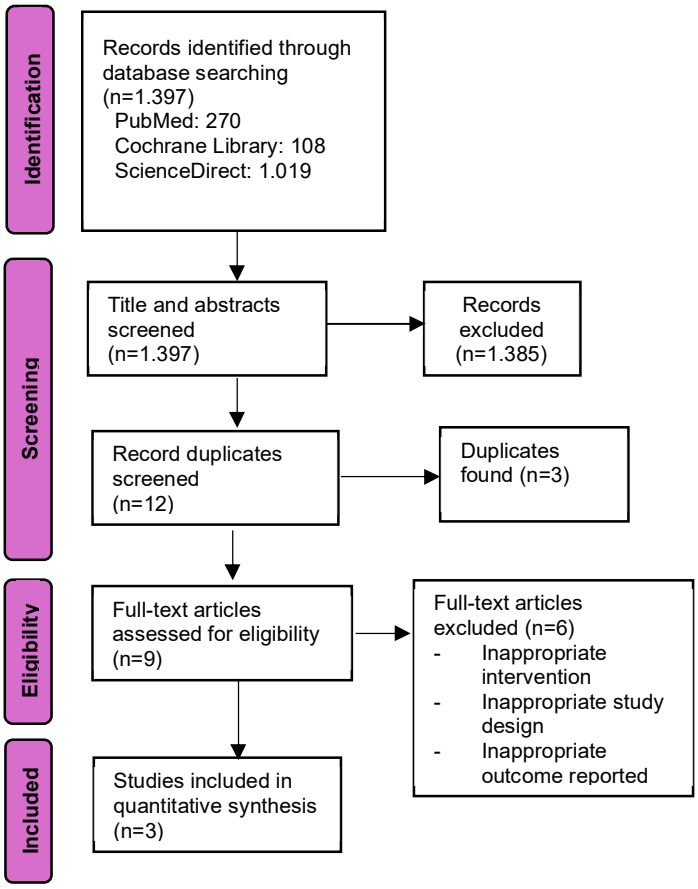

Figure 1. Flow Diagram of the literature search strategy for this meta-analysis.

RESULTS

Included Studies

The initial search obtained 1.397 research studies from all databases, but 1.385 were excluded after screening the titles and abstracts. In addition, 3 were duplicated and excluded. Approximately 6 were also excluded because the outcome was not relevant, while 3 were included for quantitative synthesis.

Quantitative Synthesis

Figure 2 presents the mean difference in the HbA1c level between the normal thyroid and abnormal group. The MD of the onset of HbA1c between both groups was 1.94 (95%CI 0.73 - 3.14; p<0,000001), with high heterogeneity reported by an I^2 of 98%. This result showed that T2DM patients with thyroid dysfunction had a significantly higher HbA1c.

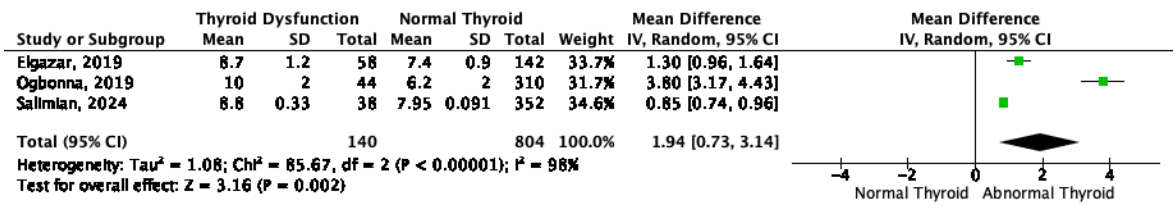

Figure 2. Forrest plot of HbA1c levels in normal thyroid patients and abnormal thyroid patients.

Table 1. Study Characteristics and Main Findings of Included Studies

Author (Year)	Country / Setting	Study Design	Population (T2DM Patients)	Sample Size (n)	Thyroid Dysfunction Type	Outcomes Measured	Main Findings	Risk of Bias
Elgazar et al. (2019)	Tanta University Hospital, Egypt	Cross-sectional comparative study	Adults aged 30–65 years with T2DM attending outpatient clinic; healthy controls included	200 T2DM patients and 200 controls	Overt hypothyroidism (7%), Subclinical hypothyroidism (13%), Overt hyperthyroidism (3%), Subclinical hyperthyroidism (6%)	Fasting blood glucose, 2-h post-prandial glucose, HbA1c, TSH, FT3, FT4, thyroid antibodies (anti-TPO, anti-Tg)	Thyroid dysfunction prevalence 29% in diabetics vs 5% in controls. Poor glycemic control (HbA1c ≥8%) and longer diabetes duration were associated with higher thyroid dysfunction. HbA1c positively correlated with TSH (p=0.033) and negatively with FT3 (p=0.004).	Low risk (adequate sample size, clear criteria, control group used, ethical approval obtained)
Ogbonna et al. (2019)	University of Nigeria Teaching Hospital, Enugu, Nigeria	Descriptive cross-sectional study	Adults ≥40 years with T2DM attending diabetes clinic or medical wards; controls without DM	354 T2DM, 118 controls	Primary hypothyroidism, subclinical hypothyroidism, hyperthyroidism, subclinical hyperthyroidism	HbA1c, fT3, fT4, TSH	Mean HbA1c significantly higher in T2DM (7.8±2.0%) vs controls (5.8±1.2%). T2DM patients with thyroid dysfunction had higher HbA1c (8.1±1.9%) than euthyroid patients (5.1±1.2%, p=0.001). HbA1c positively correlated with the presence of thyroid dysfunction (β=1.89, p=0.001) and inversely with fT3 (r=−0.6, p=0.001). Female gender, longer DM duration (>5 years), central obesity, and nephropathy were independent predictors of thyroid dysfunction.	Low risk (adequate design, ethics approval, regression analysis, representative sampling)
Salimian et al. (2024)	Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran	Cross-sectional descriptive study	Adults aged 35–65 years with confirmed T2DM attending Yazd Diabetes Center	411	Hypothyroidism (9.24%), Hyperthyroidism (5.10%)	Fasting Blood Sugar (FBS), HbA1c, TSH, T4	Prevalence of thyroid disorders: 14.3% (38 hypothyroid, 21 hyperthyroid). HbA1c significantly higher in patients with thyroid dysfunction (8.8 ± 0.33%) vs euthyroid (7.95 ± 0.09%; P = 0.021). No significant difference in FBS (P = 0.196), gender, or duration of diabetes. Authors recommend routine thyroid screening in T2DM for improved glycemic control.	Low risk (clear inclusion/exclusion, random sampling, ethical approval, appropriate statistical tests)

Qualitative Synthesis

In addition to HbA1c, several studies also reported fasting and post-prandial glucose levels to further evaluate glycemic status among patients with thyroid dysfunction. Elgazar et al. (2019) and Salimian et al. (2024) found higher fasting blood glucose levels in diabetic patients with thyroid dysfunction compared to euthyroid individuals, although only Elgazar et al. demonstrated a statistically significant difference. Post-prandial glucose levels were reported exclusively by Elgazar et al., showing significantly higher mean values in subjects with thyroid dysfunction. Ogbonna et al. (2019) did not present fasting or post-prandial glucose data but consistently demonstrated elevated HbA1c values in the thyroid dysfunction subgroup. Collectively, these findings suggest that thyroid abnormalities, particularly hypothyroidism, may exacerbate glycemic instability through altered glucose absorption, hepatic gluconeogenesis, and peripheral insulin sensitivity. However, due to variations in reporting and measurement methods, quantitative pooling of fasting and post-prandial glucose outcomes was not feasible, and a narrative synthesis approach was adopted for these parameters.

DISCUSSION

The frequency of thyroid dysfunction in Australian patients with diabetes, including type 1, type 2, and latent autoimmune diabetes, was recently investigated by Peters et al., who included comprehensive background information.[14] After the exclusion of patients with T2DM from those with known thyroid illness, the prevalence of subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism, and overt hyperthyroidism was 4.9%, 1.2%, 0.1%, and 0.2%, respectively.[14]

The ratio of fT3 to fT4 is affected by insulin sensitivity. Ferrannini et al. discovered a negative correlation between the fT3/fT4 ratio and insulin sensitivity, as measured by the clamp method in research including 940 non-diabetic patients with normal thyroid function.[15] Similarly, Park et al. identified a correlation between the fT3/fT4 ratio as well as the parameters of metabolic syndrome and insulin resistance in a cohort of 132,346 people who participated in medical health check-ups.[16] The precise mechanism through which insulin sensitivity affected the fT3/fT4 ratio remained unclear. Research suggested that decreased insulin action reduced T3 production from T4 in animal models. The less pronounced correlation between the fT3/fT4 ratio and serum CPR levels supported the hypothesis. Additionally, a very weak association was reported between the fT3/fT4 ratio and osteocalcin levels, a marker commonly used to assess bone turnover in clinical practice. Osteocalcin has also been implicated in the regulation of glucose homeostasis, with research indicating a relationship between serum osteocalcin levels and insulin secretion. Therefore, the observed connection between fT3/fT4 and osteocalcin levels may be indirectly influenced by insulin levels.[6]

DM reduces the conversion of T4 to T3 in peripheral tissues and interferes with the hypothalamic regulation of TSH release. Reduced T3 and elevated T4 are the results of severe hyperglycemia. Additionally, elevated insulin connected to DM increases TSH turnover, raises FT4, and decreases T3 by preventing the liver from converting T4 to T3.[4]

Several investigations found a favorable correlation between serum TSH, insulin resistance, and hyperglycemia in euthyroid patients.[17,18] In human adipose tissue, TSH may directly influence metabolic parameters and promote the release of leptin.[19,20] The stimulatory effects on hepatic glucose production in vitro and in vivo play a significant role in metabolism.[21,22] In a mouse liver, TSH raises the mRNA expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphate.[22] Meanwhile, TSH increases serum blood glucose levels by decreasing insulin production and synthesis in pancreatic β cells.[19] An essential neuroendocrine modulator of the hypothalamic-pituitary-thyroid (HPT) axis known as leptin works directly and indirectly by controlling the expression of the TRH gene in the paraventricular (PVN) and arcuate nucleus (ARC).[19] Patients with hypothyroidism have higher leptin levels, which are correlated with TSH.[19] Several diabetic patients have higher levels of leptin, which may

increase the production of TSH by influencing the HPT axis through the Janus activating kinase (JAK)-2/signal transducer and activator of transcription (STAT)3 factor.[23]

Few prospective studies have examined the connection of serum TSH and THs to an increased risk of acquiring T2DM. Jun et al. evaluated the relationship between the occurrence of T2DM over a 6-year follow-up and successive increases in serum TSH from baseline values in a large longitudinal study on a euthyroid population without diabetes.[24] With every 1 mU/L increase in serum TSH, the risk of incident T2DM increased significantly, according to Cox proportional hazard models. This risk was higher in subjects with the highest TSH change tertile (hazard ratio, 1.25; 95% CI, 1.05 to 1.48; P for trend = 0.011). Glycated hemoglobin (HbA1c) is the primary measure of the average glycemic control over two to three months, which changes due to variations in serum TSH.[24] In a 7-year longitudinal analysis of 6235 euthyroid patients without T2DM, individual fluctuations in TSH and THs within the normal reference range were an additional risk factor.[25] Regardless of sex or thyroid autoimmunity, a gradual increase in TSH accompanied by a decrease in T3 and fT4 was independently connected to the chance of developing T2DM. This suggested the development of a more severe type of hypothyroidism. A greater risk of T2DM was connected to an increase in TSH from baseline (range, –4.1 mU/L to +12.3 mU/L) (HR, 1.27; 95% CI, 1.14 to 1.40 per SD). A reduced probability of T2DM incidence was related to an increase in FT4 (range: –0.60 to +1.60 ng/dL) or T3 (range: –76.5 to +223 ng/dL). Insulin production, intracellular glucose availability, and islet β-cell mass are directly increased by T3.[26] These results show that within the normal range, minute variations in serum TSH and TH levels lead to insulin resistance or diabetes.[27]

According to a recent large cross-sectional study from China, a greater incidence of T2DM in males and females was independently associated with lower fT3 and fT3/fT4 ratios, as well as higher fT4 levels.[28] After controlling for confounding variables, a greater incidence of T2DM was positively and negatively correlated with fT4 and fT3 in males and females, respectively. The lower fT3/fT4 ratio indicates low T3 syndrome in poorly managed diabetic patients or may be a sign of peripheral deiodinase activity suppression, lowering basal metabolic rate and explaining the pathophysiology of T2DM.[29] According to different research, hypothyroidism increased the incidence of diabetes (RR, 2.06; 95% CI, 1.42 to 2.99). Statin users with SHypo also had a higher risk of DM, with an RR of 1.94 (95% CI, 1.13 to 3.34) and 1.20 (95% CI, 0.52 to 2.75), respectively.[11] Mitochondrial dysfunction is a common mechanism connected to DM and TD, which can be increased by statins. Additionally, statins and hypothyroidism can cause mitochondrial dysfunction.[30] The results show that patients with hypothyroidism receiving replacement dosages of L-T4 do not have a higher risk of developing DM.[11]

Numerous studies have connected insulin resistance to subclinical hypothyroidism. This association is caused by the development of metabolic syndrome and an imbalance in lipid metabolism.[31] Thyrotoxicosis increases glycogenolysis and hepatic glucose production, causing glucose intolerance.[32] However, lower glucose production from the liver, gluconeogenesis, and decreased catabolism are the primary metabolic characteristics of hypothyroidism.

The collective findings from this review underscore a clinically relevant bidirectional relationship between thyroid dysfunction and type 2 diabetes mellitus (T2DM). Thyroid hormones play a central role in regulating glucose homeostasis by influencing hepatic glucose output, intestinal absorption, and peripheral insulin sensitivity. Hypothyroidism, by reducing glucose disposal and delaying insulin clearance, can aggravate hyperglycemia, whereas hyperthyroidism accelerates glycogenolysis and gluconeogenesis, leading to fluctuating glucose levels and poor glycemic stability. These physiological mechanisms explain the consistent observation of higher HbA1c values among diabetic patients with concomitant thyroid dysfunction across included studies.

From a clinical standpoint, these findings

emphasize the importance of routine thyroid function screening in all patients with T2DM particularly those with unexplained glycemic variability, refractory hyperglycemia despite therapy adjustment, or long-standing diabetes. Early detection and correction of thyroid abnormalities can improve metabolic balance, reduce cardiovascular risk, and optimize diabetes management outcomes. Periodic monitoring of TSH and free T4 levels should therefore be incorporated into standard diabetes care protocols, with testing intervals individualized based on comorbidity burden, age, and duration of disease.

Furthermore, the integration of multidisciplinary management involving endocrinologists, diabetologists, and primary care physicians is essential to achieve optimal patient outcomes. Pharmacological adjustments may be required, as hypothyroidism often necessitates lower insulin or oral hypoglycemic doses after levothyroxine therapy, while hyperthyroid states can increase insulin requirements. Patient education regarding symptom recognition and medication adherence should be prioritized to prevent metabolic decompensation.

In addition, pooled analysis results should be interpreted cautiously as the data were heterogeneous (I^2=98%). Finally, further prospective interventional studies are warranted to determine whether proactive thyroid hormone correction directly translates into improved glycemic control and long-term vascular outcomes in diabetic populations. Until such evidence is available, clinicians should maintain a high index of suspicion for thyroid dysfunction in any patient with erratic blood glucose control or discordant HbA1c results despite apparent therapeutic compliance.

CONCLUSION

In conclusion, thyroid dysfunction was reported to be very common among T2DM, and the frequency increased with hyperglycemia. Glycaemic management also deteriorated due to decreased TSH and T3. In this context, thyroid function was periodically monitored as part of T2DM patient care guidelines.

CONFLICT OF INTERESTS

All the authors declare that there are no conflicts of interest.

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