Review

The Intricate Relationship Between Thyroid Disorders and Type 2 Diabetes – a Narrative Review

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The Intricate Relationship Between Thyroid Disorders and Type 2 Diabetes—A narrative Review

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Abstract: Thyroid disorders (TD) and diabetes mellitus (DM) represent significant metabolic pathologies with an important global burden. Diabetes, characterized by chronic hyperglycemia, induces widespread dysregulation of lipid, protein, and carbohydrate metabolism. The thyroid gland, a central regulator of endocrine homeostasis, modulates metabolic processes through the secretion of thyroid hormones. A complex bidirectional relationship exists between type 2 diabetes mellitus (T2DM) and thyroid dysfunction, wherein each condition may exacerbate the pathophysiological consequences of the other. At the core of this interplay lies insulin resistance, a fundamental mechanism underlying their coexistence and mutual aggravation. A comprehensive understanding of the physiological, biochemical, and molecular mechanisms would undoubtedly uncover new perspectives on T2DM, particularly concerning thyroid status alterations. Grasping the clinical correlation between these widespread endocrine disorders is crucial for customizing treatments for individuals confronting both conditions. This narrative review seeks to offer an understanding of the epidemiological, pathophysiological, and clinical dimensions of the relationship between thyroid dysfunction and type 2 diabetes mellitus. Considering the substantial clinical ramifications of concurrent T2DM and TD, it is imperative to institute suitable screening and management approaches for both endocrine disorders to guarantee optimal care for patients.

Keywords: type 2 diabetes mellitus; insulin resistance; hypothyroidism; hyperthyroidism; thyroid disorders

1. Introduction

Diabetes mellitus (DM) is one of the the most prevalent non-transmissible chronic diseases, arising due to the malfunction of pancreatic β cells, frequently on the background of insulin resistance. With swift economic progress, profound shifts in lifestyles, and an aging demographic, type 2 diabetes mellitus (T2DM) has emerged as a prominent public health challenge worldwide, particularly in developing nations. As per the most recent data from the International Diabetes Federation (IDF), the global prevalence of T2DM among adults reached 536.6 million individuals (10.5%) in 2021. Projections indicate that by 2045, there will be 783.2 million people (12.2%) living with diabetes globally [1,2].

On the other hand, thyroid dysfunction is commonly reported in the general population. Overt hypothyroidism affects approximately 0.2% to 5.3% of the European population and 0.3% to 3.7% of individuals in the USA, depending on the diagnosis criteria and studied demographics. Large-scale longitudinal studies in the UK reveal an incidence rate of 3.5–5.0 per 1000 for women and 0.6–1.0 per 1000 for men in spontaneous hypothyroidism. [3,4]

On the flip side, the prevalence of overt hyperthyroidism ranges from 0.2% to 1.3% in iodine-sufficient regions globally. In the United States National Health and Nutrition Examination Survey (NHANES III), overt hyperthyroidism was identified in 0.5% of the population, with an additional

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0.7% having subclinical hyperthyroidism, leading to an overall prevalence of 1.3%. Similar rates have been reported in studies from various countries such as Sweden, Denmark, Norway, and Japan. A meta-analysis of European studies estimated a mean prevalence rate of 0.75% and an incidence rate of 51 per 100,000 per year. [3,5]

The interplay between diabetes and thyroid dysfunction has been a subject of research for decades [6]. Researchers have predominantly delved into the prevalence of thyroid disease among individuals with type 1 diabetes, considering its autoimmune origin. In contrast, the association between type 2 diabetes and thyroid disorders has remained relatively understudied.

2. Materials and Methods

This review was carried out with a survey of the different scientific articles related to the theme, with a critical and comparative analysis of these articles. We used the following strategy to search the U.S. National Library of Medicine's PubMed database and Google Scholar for relevant articles published over the past 20 years , including prospective studies on the association between thyroid function (hormone levels), risk of T2DM, and prospective studies of the linkage between thyroid function and IT. Keywords included: “thyroid dysfunction and type 2 diabetes mellitus”, “hypothyroidism and type 2 diabetes mellitus”, “hyperthyroidism and type 2 diabetes mellitus”. The Boolean logical operator AND was used to combine the diabetes and thyroid function terms, and operator OR between terms within those categories. All searches were limited to English language and adults. Additionally, references of related articles and current review articles were manually screened for potentially relevant articles.

We performed a thorough review of recommended thyroid screening guidelines for individuals with type 2 diabetes mellitus (T2DM) from leading diabetes and endocrinology organizations. This step was crucial for understanding current best practices in assessing thyroid function in T2DM. Integrating these guidelines into clinical protocols can improve the detection of thyroid issues in diabetic patients, especially those with complex medical histories. By aligning with established recommendations, we aim to enhance patient care, accuracy in diagnosis, and timely intervention for thyroid abnormalities in T2DM. Our focus was on articles providing insights into thyroid disease incidence, epidemiology and risk factors, particularly hypothyroidism in T2DM patients.

3. Results

3.1. Unravelling the Prevalence of Thyroid Dysfunction in Type 2 Diabetes

Certain investigations propose a reciprocal impact of diabetes and thyroid disorders on each other. The Third National Health and Nutrition Examination Survey (NHANES III), a substantial cross-sectional survey comprising 17,353 participants in the USA, uncovered that hypothyroidism affected 4.6% of the study cohort, while hyperthyroidism affected 1.3% of participants. Furthermore, NHANES III noted an increased prevalence of thyroid dysfunction in individuals with diabetes in comparison to those without diabetes [7].

Certain studies have indicated a greater prevalence of thyroid dysfunction in patients with type 2 diabetes compared to the general population, with varying estimates across studies. The data from selected studies regarding the prevalence of hypo/hyperthyroidism in T2DM subjects are presented in Table 1 [8–17].

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Table 1. Comparison of studies introduced in current research containing information on the relationship between thyroid dysfunction and type 2 diabetes mellitus.

First author, Title	T2DM participants	Hypothyroidism (subclinical + overt)	Hyperthyroidism (subclinical + overt)
Adi H Khassawneh "Prevalence and predictors of thyroid dysfunction among type 2 diabetic patients: A case-control study"[8]	998	220 (22,04%)	46 (4,61%)
Syeda Iffat Bukhari "Prevalence and predictors of thyroid dysfunction amongst patients with Type 2 diabetes mellitus in Pakistan"[9]	317	82 (25,8%)	35 (11%)
"Association between glycemic status and thyroid dysfunction in patients with type 2 diabetes mellitus"[10]	354	44 participants – thyroid dysfunction (12.4 %)	
"Hypothyroidism among Type 2 Diabetic Patients Visiting Outpatient Department of Internal Medicine of a Tertiary Care Centre: A Descriptive Cross-sectional Study"[11]	384	127 (33.07%)	No data
"Prevalence of subclinical hypothyroidism in women with type 2 diabetes"[12]	410 (women)	37 (9%) *just subclinical	No data
Pranav Kumar Raghuwanshi "Evaluation of thyroid dysfunction among type 2 diabetic patients"[13]	40	10 (25%)	1 (2,5%)
Vadivelan Mehalingam "Thyroid dysfunction in patients with type 2 diabetes mellitus and its association with diabetic complications"[14]	331	46 (13,9%)	12 (3,6%)
Essmat Hassan Elgazar "Thyroid dysfunction prevalence and relation to glycemic control in patients with type 2 diabetes mellitus"[15]	200	40 (20%)	18 (9%)
S. A. Paul Chubb "The relationship between thyroid dysfunction, cardiovascular morbidity and mortality in type 2 diabetes: The Fremantle Diabetes Study Phase II"[16]	1250	76	3
Imam Subekti "Thyroid Dysfunction in Type 2 Diabetes Mellitus Patients"[17]	303	23 (7,6%)	7 (2,3%)
Subhodip Pramanik, "Thyroid Status in Patients with Type 2 Diabetes Attending a Tertiary Care Hospital in Eastern India"[18]	100	26 (26%)	0 (0%)
Biju Shrestha "Hypothyroidism among Type 2 Diabetic Patients Visiting Outpatient Department of Internal Medicine of a Tertiary Care Centre: A Descriptive Cross-sectional Study"[19]	384	127 (33,07%)	No data

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3.2. Thyroid Hormones and Glucose Metabolism: Insights into Type 2 Diabetes Pathogenesis

The immediate regulation of cellular metabolic processes relies heavily on the interplay between insulin and glucagon, two hormones released by the beta and alpha cells located in the pancreatic islets. However, a substantial body of evidence indicates the significant impact of thyroid hormones on the maintenance of glucose levels in the body, with their collective effects alongside insulin determining the specific metabolic pathways for glucose and lipids. For instance, both triiodothyronine (T3) and insulin seem to modulate the activities of key regulatory proteins responsible for glucose uptake into cells, as well as those crucial for the metabolic cascades of glucose and lipids. Previous literature reviews extensively detail the effects of insulin and thyroid hormones on various tissues of the body. Thyroid hormones demonstrate both insulin-like actions and actions that oppose insulin in multiple organs. These actions are usually finely balanced and any deficiency or excess of thyroid hormones can disrupt this balance, leading to disturbances in carbohydrate metabolism. [20,21]

Conversely, diabetes can affect thyroid function in various ways. In diabetes, the response of thyroid-stimulating hormone (TSH) to thyrotropin-releasing hormone can become impaired, leading to hypothyroidism and subsequently lower levels of T3. This decrease in T3 levels might also be due to reduced conversion of T3 from T4 in diabetes, as evidenced by studies showing a reversible decrease in deiodinase activity and hepatic thyroxine concentration induced by hyperglycemia.

On the other hand, there are studies suggesting that a short-term excess of T3 could induce insulin resistance, potentially contributing to the development of type 2 diabetes mellitus.[22]

The relationship between thyroid hormone levels and the risk of T2DM, however, remains a highly debated topic in the scientific community. Human studies have presented conflicting findings, with some reports indicating a positive association between elevated TSH and lower free thyroxine levels with hyperglycemia and insulin resistance. Conversely, other studies have found no such relationship in their research [23–26]. Therefore, it has become apparent that a comprehensive evaluation of the association between TSH, free thyroxine and T2DM is needed. Moreover, virtually all previous analyses have focused on examining the influence of baseline levels of TSH and free thyroxine on the risk of developing T2DM. [27–31]

3.3. Thyroid Dysfunction and Insulin Resistance: Partners in Type 2 Diabetes Pathogenesis?

Insulin resistance (IR) denotes a state wherein the responsiveness of target cells to regular levels of insulin is diminished. This state often coexists with an array of metabolic and cardiovascular abnormalities, collectively termed as "insulin resistance syndrome".

The prevalent forms of human IR typically align with obesity and physical inactivity, yet pinpointing a singular cellular basis for these conditions continues to elude researchers.

T2DM results from pancreatic β-cell dysfunction, frequently on the background of insulin resistance, and is explained by genetic, environmental, and metabolic factors. Persistent overnutrition drives hyperinsulinemia, β-cell failure, and disease progression, with obesity—particularly visceral and hepatic fat—being a key contributor. IR impairs β-cell insulin secretion, increases lipolysis and elevates non-esterified fatty acids (NEFA), further disrupting the metabolic balance. Beyond glycemic control, IR is independently linked to macrovascular and microvascular complications, including diabetic cardiomyopathy and chronic kidney disease. [32]

Both hypothyroidism and hyperthyroidism have been associated with insulin resistance, mirroring the impaired glucose metabolism observed in T2DM. [33,34]

Thyroid hormones are integral to glucose metabolism and insulin sensitivity, with their dysregulation contributing to insulin resistance in both hypo and hyperthyroid states. In hyperthyroidism, elevated thyroid hormone levels enhance hepatic glucose production and turnover, leading to hepatic IR and impaired glucose tolerance. Conversely, hypothyroidism is associated with IR predominantly in peripheral tissues, such as skeletal muscle and adipose tissue, resulting in decreased glucose uptake and utilization. These alterations in insulin sensitivity underscore the critical role of thyroid function in maintaining metabolic homeostasis and highlight the importance

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of monitoring and managing IR in patients with thyroid disorders to prevent the progression of metabolic complications. [34]

In a study by Maratou et al., patients with overt hypothyroidism and subclinical hypothyroidism presented a decreased level of insulin-stimulated glucose transport in monocytes due to disrupted translocation of the GLUT4 — glucose transporter in the plasma membrane. [35]

Patients with overt hyperthyroidism (HR) and subclinical hyperthyroidism (SHR) in the same study[35] also presented an increased level of baseline density of the GLUT4 and GLUT3 transporters. The increased expression of the GLUT3 and GLUT4 glucose transporters at the baseline insulin levels reflects the ability of monocytes to 'cope' with the increased rate of metabolism associated with this condition. [36]

Another potential pathogenetic mechanism for the development of insulin resistance in hypothyroidism is associated with a decreased blood flow in peripheral tissues. [37]

Independently on their etiology, both hypo and hyperthyroidism may affect glucose regulation in diabetic patients as well as in non-diabetic subjects. [38]

3.4. Hypothyroidism and T2DM: Is There a Link Between Type 2 Diabetes and Hypothyroidism?

Hypothyroidism is the most common thyroid disorder in the adult population. Studies have found a higher prevalence of overt hypothyroidism in the type 2 diabetic population than in the general population, but the relationship between subclinical hypothyroidism and T2DM is still controversial. The coexistence of type 2 diabetes and hypothyroidism is an emerging trend observed in clinical practice. Although the effects of isolated T2DM and hypothyroidism are well known, limited studies addressed the metabolic complications when these two conditions co-exist.

Thyroid hormones exert a direct influence on insulin secretion. Hypothyroidism resulted in a decrease in beta cell insulin production whereas hyperthyroidism led to an increase in beta-cell responsiveness to catecholamine or glucose due to increased beta-cell mass. Additionally, thyrotoxicosis increases insulin clearance. All of these changes occur as a result of alternations in thyroid hormone which increases the risk of developing T2DM and can lead to diabetic complications or can worsen diabetic symptoms [39–42].

Hypothyroidism is characterized by decreased glucose absorption from the gastrointestinal tract, extended peripheral glucose buildup, gluconeogenesis, decreased hepatic glucose production and decreased glucose disposal [43]. Hypothyroidism can affect glucose metabolism in T2DM in different ways. For example, subclinical hypothyroidism can result in insulin resistance due to a decreased rate of insulin-stimulated glucose transfer induced by a translocation of the GLUT 2 gene. Additionally, according to a recent study, due to decreased insulin clearance by the kidneys, the physiological need for insulin was decreased in hypothyroidism. Moreover, anorectic circumstances may also contribute to lower insulin production in hypothyroidism.[44]

Also, insulin resistance has been associated with hypothyroidism in multiple preclinical and in vitro studies [45], demonstrating reduced insulin sensitivity in peripheral muscle tissues under hypothyroid conditions. In addition, dysregulated leptin metabolism has been proposed as a potential contributing factor to this pathophysiological mechanism. Additionally, several researchers have identified a direct correlation between insulin resistance and hypothyroidism. However, discrepancies in findings among some studies underscore the necessity for further investigation in this domain [44].

Thyroid hormones themselves affect metabolism and thus alter glucose homeostasis. Hypothyroidism leads to reductions in hepatic glucose output, gluconeogenesis and peripheral glucose utilization thus predisposing to hypoglycemia [18].

Explanation of variability in hypothyroidism prevalence in different diabetes populations can be made by several parameters such as adequacy of iodine intake which can affect the baseline thyroid status of the population and presence of goiter, metabolic determinants like population prevalence of glycemic disturbances, metabolic syndrome, several comorbidities related to thyroid dysfunction, and in epidemiological perspective, the total prevalence of diabetes in the population.

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In other words, studies about comorbidities of diabetes and thyroid dysfunction are population specific [17].

Subclinical hypothyroidism is associated with profound disruptions in carbohydrate and lipid metabolism, characterized by attenuated intestinal glucose absorption, prolonged peripheral glucose sequestration, upregulated hepatic gluconeogenesis, suppressed hepatic glucose output, impaired hepatic glucose utilization and dyslipidemia. These metabolic perturbations underscore the intricate interplay between thyroid function and systemic metabolic homeostasis [46].

3.4.1. Effect of hyperthyroidism on glucose metabolism

The incidence of clinically manifest type 2 diabetes mellitus has significantly increased in the context of thyrotoxicosis since Rohdenburg first showed that elevated thyroid hormone levels cause disruptions in carbohydrate metabolism and established the connection within thyroid hormones and diabetes mellitus [47]. Insulin resistance and poor regulation of glucose are commonly linked to symptomatic hyperthyroidism, with overt diabetes identified in 2-3% of cases and glucose intolerance described in around 50% of hyperthyroid patients (44).

Numerous studies have been conducted to determine the underlying mechanism of how hyper thyroidism affects the decline in glycemic control.

Hyperthyroidism can create insulin resistance through the following potential mechanisms: it increases intestinal glucose absorption, induces postprandial hyperglycemia, increases hepatic glucose output, higher levels of free fatty acids (FFAs), reduced insulin secretion, and decreased sensitivity to insulin in peripheral tissues.[34,36,48–50]

Hyperthyroidism increases glucose demand, primarily met by enhanced hepatic gluconeogenesis (fasting state) and Cori cycle activity (postprandial and fasting states). Fasting-state lipolysis elevates glycerol and nonesterified fatty acids (NEFAs), with glycerol and amino acids from proteolysis serving as gluconeogenic substrates. NEFAs stimulate gluconeogenesis and fuel oxidation in peripheral tissues. Postprandially, insulin-stimulated glucose uptake in skeletal muscle is normal or elevated due to increased perfusion, but glycogen synthesis is impaired, favoring lactate production and Cori cycle activation. This cycle acts as a glucose-lactate buffer for metabolic flexibility. Postprandial lipolysis suppression facilitates glucose utilization by insulin-resistant muscle, preserving fat stores.[51–54]

3.4.2. Role of Hepatic Glucose Output and Insulin Resistance in T2DM and Hyperthyroidism

Excessive hepatic glucose production is a critical factor in peripheral insulin resistance, glucose intolerance, and hyperinsulinemia. In thyrotoxicosis, increased glycogenolysis and hepatic glucose output contribute to impaired glucose tolerance, promoting progression from prediabetes to diabetes and exacerbating hyperglycemia in T2DM. Both T2DM and hyperthyroidism share pathophysiological mechanisms, including β-cell dysfunction, insulin resistance, altered glucagon secretion, increased intestinal glucose absorption, and elevated catecholamine levels.[40,55–58] Among these, insulin resistance represents the primary link between thyroid dysfunction and T2DM. Hepatic insulin resistance is driven by excessive glucose output rather than fasting hyperinsulinemia, and elevated hepatic glucose production is a major determinant of increased fasting plasma glucose in T2DM. [36,44] Skeletal muscle insulin resistance further disrupts glucose homeostasis, contributing to metabolic deterioration.[32,59] Additionally, insulin resistance influences lipid metabolism, reinforcing the link between thyroid dysfunction and T2DM.[57,60,61]

3.5. Genetic Influences on Thyroid Function and Glucose Metabolism

Thyroid hormones (TH) significantly influence glucose metabolism through genetic regulation of various metabolic pathways. Key genes involved include mitochondrial uncoupling proteins (UCP-3), glucose transporters (GLUT-4, GLUT-1), and PGC-1α. Triiodothyronine (T3) enhances GLUT-4-mediated glucose transport, while UCP-3 affects fatty acid oxidation and glucose

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metabolism. Thyroid hormone receptors (TRα1, TRβ1, TRβ2) modulate metabolic processes, with TRβ isoforms maintaining hypothalamic-pituitary-thyroid axis homeostasis.[61,62]

Genetic factors substantially determine thyroid function and glucose metabolism. Studies indicate that up to 67% of circulating thyroid hormone and thyrotropin (TSH) concentrations are genetically determined, suggesting a genetic 'set point' for individual thyroid function. [62]

Additionally, genetic factors account for an estimated 58–71% of the inter-individual variation in TSH and free thyroxine (FT4) concentrations.[63]

Deiodinases (D1, D2, D3) regulate T3 bioavailability, impacting insulin responsiveness. Variants such as Thr92Ala in D2 are associated with insulin resistance and altered glucose turnover in skeletal muscle and adipose tissue.[64–66] Furthermore, hyperthyroidism enhances GLUT-2 expression, lipid peroxidation, and catecholamine-mediated lipolysis, disrupting lipid metabolism and reinforcing insulin resistance.

In summary, genetic influences on thyroid function significantly impact glucose metabolism through the regulation of key metabolic genes and pathways. Understanding these genetic interactions is crucial for developing targeted therapeutic strategies for metabolic disorders involving thyroid dysfunction and impaired glucose metabolism.

Table 2 highlights studies from the literature that substantiate the bidirectional influence between thyroid disorders and type 2 diabetes, reinforcing the complex interplay between these conditions.

Table 2. Bidirectional Relationship Between Thyroid Dysfunction and Type 2 Diabetes: A Review of Key Studies.

First author, Title	Publication year	Type	Key Findings
Biju Shrestha "Hypothyroidism among Type 2 Diabetic Patients Visiting Outpatient Department of Internal Medicine of a Tertiary Care Centre: A Descriptive Cross-sectional Study"[19	2023	A Descriptive Cross-sectional Study	A total of 384 subjects with type 2 diabetes participated in the study using convenience sampling. Hypothyroidism prevalence was 33.07% (95% CI: 28.36-37.78) among the patients, with 56 (44.09%) males and 71 (55.90%) females. Mean age was 55.17±7.53 years. Hypothyroidism prevalence exceeded rates from similar studies in comparable settings [19].
Syeda Iffat Bukhari "Prevalence and predictors of thyroid dysfunction amongst patients with Type 2 diabetes mellitus in Pakistan"[9]	2022	Descriptive cross-sectional study	The occurrence of thyroid dysfunction is elevated among individuals with type 2 diabetes mellitus (T2DM), with hypothyroidism emerging as the predominant dysfunction, particularly prevalent among female patients [9].
The relationship between thyroid dysfunction, cardiovascular morbidity and mortality in type 2 diabetes: The Fremantle Diabetes Study Phase II S. A. Paul Chubb1,2	2022		Summary: This study included 1,250 participants with type 2 diabetes, without known thyroid disease or medications affecting thyroid function. Participants were classified based on their baseline serum free thyroxine (FT4) and thyrotropin (TSH) levels into euthyroid, overt hypothyroidism (increased TSH, low FT4), subclinical hypothyroidism (increased TSH, normal FT4), overt thyrotoxicosis (decreased TSH, raised FT4), or subclinical thyrotoxicosis (decreased TSH, normal FT4) groups. Over a 6.2 to 6.7 year follow-up, incident myocardial infarction, stroke, all-cause mortality, and cardiovascular mortality were tracked. The results showed that most participants with newly detected thyroid dysfunction had subclinical hypothyroidism (77.2%), with overt/subclinical thyrotoxicosis being rare. When compared to participants with TSH levels between 0.34-2.9 mU/L, those with TSH levels > 5.1 mU/L did not have an increased risk of incident myocardial infarction

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			(adjusted hazard ratio 1.77), stroke (1.66), all-cause mortality (0.78), or cardiovascular mortality (1.16). Baseline factors independently associated with subclinical hypothyroidism included estimated glomerular filtration rate and systolic blood pressure. In conclusion, despite its association with cardiovascular disease risk factors, subclinical hypothyroidism was not independently linked to cardiovascular events or mortality in individuals with type 2 diabetes living in the community. [16]
Fen Rong "Association between thyroid dysfunction and type 2 diabetes: a meta-analysis of prospective observational studies"[31]	2021	Research Article	In summary, our meta-analysis has demonstrated an association between thyroid dysfunction and an elevated risk of developing T2DM. However, the evidence does not support an association between thyroid dysfunction and cardiovascular disease (CVD) events or overall mortality in individuals with T2DM, despite the limited number of studies available. Consequently, the measurement of TSH levels in individuals with risk factors for diabetes may assist in the further assessment of T2DM risk [31].
Adi H Khassawneh "Prevalence and predictors of thyroid dysfunction among type 2 diabetic patients: A case-control study"[8]	2020	Case-Control Study	A considerable number of T2DM patients were found to have thyroid disorders. Hence, we propose regular screening for thyroid dysfunction in diabetic patients. Among T2DM patients, advanced age, female gender, goiter, and poorly managed diabetes were identified as risk factors for thyroid dysfunction. Therefore, effective management and control of diabetes could potentially reduce the risk of thyroid dysfunction, and vice versa[8].
Vadivelan Mehalingam "Thyroid dysfunction in patients with type 2 diabetes mellitus and its association with diabetic complications"[14]	2020	Original article	Among 331 patients with type 2 diabetes mellitus, 13.9% had hypothyroidism and 3.6% had hyperthyroidism. Females showed a higher prevalence of thyroid dysfunction. No correlation was found between thyroid dysfunction and diabetic complications. Overall, the prevalence of thyroid dysfunction in these patients was 17.5% [14]
SU Ogbonna "Association between glycemic status and thyroid dysfunction in patients with type 2 diabetes mellitus"[10]	2019	Original Research	In this study, 354 type 2 diabetes mellitus (T2DM) patients and 118 non-diabetic controls were examined. Results showed higher HbA1c levels in T2DM patients compared to controls (7.8±2.0% vs 5.8±1.2%, p=0.001), and lower fT3 levels (2.3±1.5 pg/mL vs 2.7±2.2 pg/mL, p=0.03). T2DM patients with thyroid dysfunction had even higher HbA1c levels (8.1±1.9% vs 5.1±1.2%, p=0.001), showing a positive linear relationship with thyroid dysfunction (regression coefficient=1.89, p=0.001). In conclusion, this study indicates a direct link between HbA1c levels and thyroid dysfunction in T2DM patients. It also suggests an inverse correlation between HbA1c levels and serum fT3 concentrations, emphasizing the significance of assessing thyroid function in managing T2DM [10].
Teresa Dalla Zuanna "A Systematic Review of Case-Identification Algorithms Based on Italian Healthcare Administrative Databases for Two Relevant Diseases of the Endocrine System: Diabetes Mellitus and Thyroid Disorders"[67]	2019	Systematic Review	The systematic review examined algorithms for identifying cases of diabetes mellitus (DM) and thyroid disorders (TD) using Italian healthcare administrative databases. It found that while numerous algorithms exist for DM, they are often similar and lack clinical justification for their differences. In contrast, literature on TD identification is limited. The review concluded that further validation and implementation of these algorithms are necessary to enhance their accuracy and applicability[67].

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Essmat Hassan Elgazar "Thyroid dysfunction prevalence and relation to glycemic control in patients with type 2 diabetes mellitus"[15]	2019	cross-sectional study	Summary: A cross-sectional study of 200 patients with T2DM and 200 healthy controls assessed various parameters including blood glucose levels, HbA1, thyroid function tests(TSH, FT3, FT4), cholesterol, triglycerides, and thyroid antibodies (anti-TPO, anti-Tg). Results showed significantly elevated TSH and T3 levels in diabetic patients compared to controls ($P < 0.001$, $P = 0.001$). TD was more prevalent in patients with HbA1c levels ≥ 8% ($P = 0.0001$) and those with longer diabetes duration ($P < 0.001$). The study concluded a higher prevalence of thyroid dysfunction in type 2 DM patients, with a correlation between poor glycemic control (higher HbA1c) and thyroid dysfunction development. Subclinical hypothyroidism was the most common type of TD observed in diabetic patients [15]
Sang Ah Lee "Association between continuity of care and type 2 diabetes development among patients with thyroid disorder"[68]	2019	Observational Study	Among 4099 patients with thyroid disorders, 1036 (25.3%) developed Type 2 Diabetes (T2D). Hyperthyroidism increases liver gluconeogenesis and peripheral insulin resistance, correlating with glucose intolerance. Hypothyroidism, however, decreases glucose intolerance and improves peripheral insulin sensitivity. Treatment for hypothyroidism enhances insulin sensitivity. Previous studies suggest hypothyroidism's indirect association with diabetes onset through metabolic syndrome. Therefore, controlling thyroid hormone levels within the normal range is imperative in patients with thyroid dysfunction to prevent the development of diabetes[68].
Rong-Hsing Chen, "Thyroid diseases increased the risk of type 2 diabetes mellitus A nation-wide cohort study"[69]	2019		A sub-dataset of the National Health Insurance Research Database (NHIRD) was used. The thyroid disease group was chosen from patients older than 18 years and newly diagnosed between 2000 and 2012. The control group consisted of randomly selected patients who never been diagnosed with thyroid disease and 4-fold size frequency matched with the thyroid disease group. The event of this cohort was T2D (ICD-9-CM 250.x1, 250.x2). The occurrence of T2D in the thyroid disease group was higher than the control group with hazard ratio (HR) of 1.23 [95% confidence interval (CI) = 1.16–1.31]. Both hyperthyroidism and hypothyroidism were significantly higher than control. Significantly higher HR was also seen in female patients. Higher occurrence of T2D was also seen in thyroid disease patients without comorbidity than in the control group with HR of 1.47 (95% CI=1.34–1.60). The highest HR was found in the half-year follow-up. There was a relatively high risk of T2D development in patients with thyroid dysfunctions, especially in the period of 0.5 to 1 year after presentation of thyroid dysfunctions.[69]
Subhodip Pramanik, "Thyroid Status in Patients with Type 2 Diabetes Attending a Tertiary Care Hospital in Eastern India"[18]	2018	Original article	In this study of 100 consecutive diabetes patients, thyroid function was assessed using clinical and biochemical markers. Subclinical hypothyroidism was found in 23% of patients, overt hypothyroidism in 3%, and positive thyroid autoantibodies in 13.1%. All patients were iodine sufficient. There was a correlation between higher TSH levels and increased neuropathy ($r = 0.45$) and decreased nephropathy ($r = -0.29$).

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			In conclusion, about one in four diabetes patients had thyroid dysfunction. Routine thyroid screening is recommended. The success of the salt iodination program in this region is noted[18].
Anas Awad Alsolami "Association between type 2 diabetes mellitus and hypothyroidism: a case–control study"[70]	2018	A case-control study	It analyzed 121 cases and 121 controls. Cases were older (P=0.005) with higher rates of T2DM (P<0.001), elevated HbA1c levels (P=0.03), and more insulin (P<0.001) and oral hypoglycemic drug use (P<0.001). They also had increased hypertension (P<0.001), coronary artery disease (CAD) (P<0.001), stroke (P=0.04), diabetic foot (P<0.001), and nephropathy (P<0.001). Multivariate analysis showed a higher risk of hypothyroidism in T2DM patients (OR=4.14; 95% CI=2.20–7.80; P<0.001) and those with CAD (OR=14.15; 95% CI=1.80–111.43; P=0.01). Conclusion: T2DM patients face increased hypothyroidism risk. Better T2DM management could mitigate this risk. Further prospective studies are warranted [70].
Ji Eun Jun, "Association between changes in thyroid hormones and incident type 2 diabetes: A seven-year longitudinal study"[71]	2017		A study enrolled 6,235 euthyroid subjects (3,619 men and 2,616 women) without diabetes who underwent thyroid function tests annually between 2006 and 2012. Changes in hormone levels were calculated by comparing baseline values with those at the end of follow-up or one year before diabetes diagnosis. Results from 25,692 person-years of follow-up revealed 229 new cases of type 2 diabetes. After adjusting for potential confounders such as HbA1c and fasting glucose, individuals in the highest tertile of TSH change (2.5 to 4.2 μIU/mL) had an increased risk of developing type 2 diabetes (hazard ratio [HR] = 1.44, 95% confidence interval [CI] 1.04-1.98, p for trend 0.027) compared to those in the lowest tertile (4.1 to 0.5 μIU/mL). In contrast, the highest tertile of T3 change (16.3 to 104.7 ng/dL) and FT4 change (0.2 to 1.6 ng/dL) were associated with a reduced risk of diabetes (HR 0.60, 95% CI: 0.43-0.85, p for trend 0.002 and HR 0.34, 95% CI: 0.24-0.48, p for trend <0.001, respectively) compared to the lowest tertile (76.5 to 1.8 ng/dL and 0.6 to 0.0 ng/dL, respectively). These associations remained significant when each hormone was analyzed as a continuous variable. However, baseline levels or tertiles of TSH and thyroid hormones were not linked to diabetes risk. Individual changes in TSH and thyroid hormones within the normal reference range were identified as additional risk factors for incident type 2 diabetes [71]
Pranav Kumar Raghuwanshi "Evaluation of thyroid dysfunction among type 2 diabetic patients"[13]	2014	Original Article	Study included 80 subjects. Results showed: - In type 2 diabetic patients: - Hypothyroidism: 10.00% - Subclinical hypothyroidism: 15.00% - Hyperthyroidism: 2.5% - In non-diabetic healthy subjects: - Hypothyroidism: 2.5% - Subclinical hypothyroidism: 7.5% Conclusion: Thyroid dysfunction was more prevalent in type 2 diabetes mellitus subjects compared to non-diabetic individuals.[13]

4. Conclusions

Due to the complex interplay between thyroid function and diabetes, it is recommended to adopt a systematic and comprehensive strategy for thyroid assessment in individuals with diabetes

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mellitus, especially those with challenging comorbidities. The management of hypo/hyperthyroidism plays a pivotal role in achieving improved control over concurrent conditions.

Identifying and addressing latent hypothyroidism in these patients stands to significantly augment their overall quality of life. Consequently, it becomes imperative to identify instances where hypothyroidism contributes to morbidity, and specifically where it underlies suboptimal management of concurrent medical conditions.

Moreover, existing literature supports the notion that thyroid dysfunction, particularly hypothyroidism, frequently coexists with diabetes mellitus, potentially exacerbating metabolic derangements and complicating therapeutic regimens. As such, routine screening for thyroid disorders in diabetic populations, especially in those exhibiting challenging clinical profiles, becomes a prudent clinical approach.

Further studies have indicated a bidirectional relationship between thyroid dysfunction and diabetes mellitus, wherein the presence of one condition may adversely affect the course and management of the other. This underscores the importance of early detection and appropriate management of thyroid dysfunction in diabetic individuals, to optimize therapeutic outcomes and mitigate potential complications.

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Abbreviations

The following abbreviations are used in this manuscript:

NHANES III	Third United States National Health and Nutrition Examination Survey
NHIRD	National Health Insurance Research Database
UCP-3	Uncoupling Proteins
GLUT	Glucose Transporter in the plasma membrane
NEFA	Noesterified Fatty Acids
T2DM	Type 2 Diabetes Mellitus
TSH	Thyroid-Stimulating Hormone
SHR	Sublinical Hyperthyroidism
FT4	Free Thyroxine
CVD	Cardiovascular Disease
TD	Thyroid Disorders
DM	Diabetes Mellitus
T3	Triiodothyronine
IR	Insulin Resistance
HR	Hyperthyroidism

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