



Links between Thyroid Disorders and Glucose Homeostasis

Young Sil Eom¹, Jessica R. Wilson², Victor J. Bernet²

¹Division of Endocrinology, Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Korea,

²Division of Endocrinology, Diabetes and Metabolism, Mayo Clinic, Jacksonville, FL, USA

Thyroid disorders and diabetes mellitus often coexist and are closely related. Several studies have shown a higher prevalence of thyroid disorders in patients with diabetes mellitus and *vice versa*. Thyroid hormone affects glucose homeostasis by impacting pancreatic β -cell development and glucose metabolism through several organs such as the liver, gastrointestinal tract, pancreas, adipose tissue, skeletal muscles, and the central nervous system. The present review discusses the effect of thyroid hormone on glucose homeostasis. We also review the relationship between thyroid disease and diabetes mellitus: type 1, type 2, and gestational diabetes, as well as guidelines for screening thyroid function with each disorder. Finally, we provide an overview of the effects of antidiabetic drugs on thyroid hormone and thyroid disorders.

Keywords: Diabetes mellitus; Glucose; Homeostasis; Thyroid diseases; Thyroid hormones

INTRODUCTION

Thyroid disorders and diabetes mellitus (DM) are common chronic endocrine disorders that often coexist. A higher prevalence of thyroid disorders is seen in patients with type 1 diabetes mellitus (T1DM) [1] and type 2 diabetes mellitus (T2DM) compared to the general population [2,3]. In addition, a higher prevalence of DM is noted in patients with thyroid disorders [4-6]. While increased medical surveillance in patients with DM or thyroid disorders may account for this trend, potential pathophysiological mechanisms do exist that might explain the development of thyroid disorders in patients with DM and also the increased risk for development of DM in individuals with thyroid disorders. Autoimmunity is an important element for understanding the linkage between T1DM and autoimmune thyroid disease (AITD) while the relationship between T2DM and thyroid disorders is more complex. The aim of this article is to review the links between alterations in glucose ho-

meostasis, including diabetes, as related to the presence of thyroid dysfunction.

GLUCOSE HOMEOSTASIS AND THYROID HORMONE

Glucose homeostasis

Plasma glucose levels are balanced by glucose entry and removal from the circulation. Glucose entering the circulation is derived from intestinal absorption during the fed state, glycogenolysis and gluconeogenesis. The rate of gastric emptying mainly determines the rate of glucose appearance in the circulation while hepatic breakdown of glycogen (glycogenolysis) and formation of glucose from non-carbohydrate substrates such as lactate, amino acids, and glycerol (gluconeogenesis) are other important sources of circulating glucose [7]. Glucose homeostasis is the tight regulation of blood glucose levels critical to maintain life in mammals. This is achieved by a balance of

Corresponding author: Victor J. Bernet <https://orcid.org/0000-0002-2477-5631>
Division of Endocrinology, Diabetes and Metabolism, Mayo Clinic, 4500 San Pablo
Road, Jacksonville, FL 32224, USA
E-mail: Bernet.Victor@mayo.edu

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hormone and neuropeptides released from the brain, pancreas, liver, intestine, adipose, and muscle tissue [8]. Insulin and glucagon are the most important hormones for glucose homeostasis. Insulin is a pancreatic β -cell hormone that lowers blood glucose concentration in three ways: (1) promoting glucose uptake by the cells of insulin-sensitive peripheral tissues, including skeletal muscle and adipocytes; (2) promoting storage of glucose as glycogen, or conversion to fatty acids in the liver; and (3) suppression of postprandial glucagon secretion [7]. Glucagon is secreted from pancreatic α -cells and plays a major role in sustaining plasma glucose during the fasting state. When plasma glucose level falls below the normal level, glucagon secretion rises, leading to hepatic glucose production and return of plasma glucose to normal range [9]. Glucose homeostasis is also regulated by other glucoregulatory hormones like amylin, glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), epinephrine, cortisol, and growth hormone (GH). Amylin is isolated from pancreatic amyloid deposits and co-secreted with insulin by pancreatic β -cells in response to nutrient stimuli [10]. Amylin suppresses postprandial glucagon secretion, slows gastric emptying and reduces food intake and body weight [7]. GLP-1 and GIP, incretin hormones are secreted by intestinal L-cells. GIP stimulates insulin secretion but does not inhibit glucagon secretion or gastric emptying.

GLP-1 not only stimulates glucose-dependent insulin secretion but also suppresses postprandial glucagon secretion. It also slows gastric emptying and reduces food intake and thereby body weight [11]. Blood glucose levels can also be sensed by the central nervous system [12]. In response to low plasma glucose, the ventromedial hypothalamus triggers release of counterregulatory hormones [13]. After a meal, glucose is absorbed and plasma glucose levels rise. Increasing glucose levels stimulate pancreatic β -cells to secrete insulin. Insulin increases glucose disposal by glycogen synthesis and lipogenesis in the liver, and promotes the uptake of glucose and conversion to glycogen or triglycerides by skeletal muscle and adipose tissue. In contrast, during a fasting state, glucagon is released to increase blood glucose levels through glycogenolysis. When fasting is prolonged, glucose is produced by hepatic gluconeogenesis (Fig. 1) [7].

The effects of thyroid hormone on glucose homeostasis

Thyroid hormone (TH) has long been known to affect glucose homeostasis. TH has been reported to be related to pancreatic β -cell development and influence glucose metabolism through several organs such as the liver, gastrointestinal tract, pancreas, adipose tissue, skeletal muscles, and the central nervous system (Fig. 2).

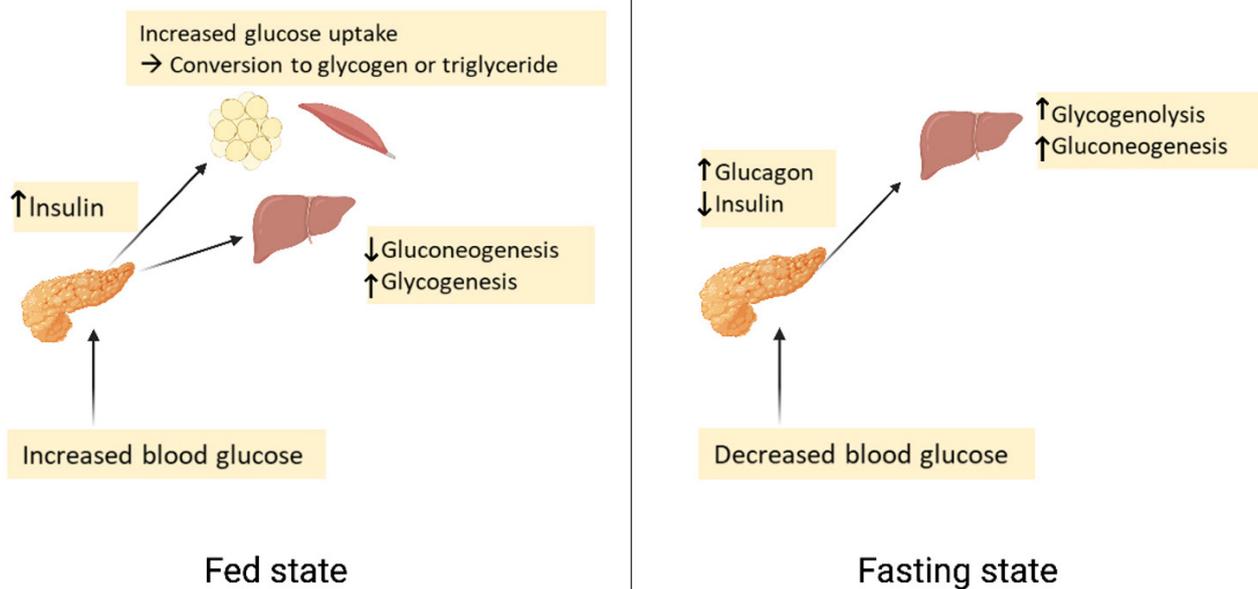


Fig. 1. Maintenance of blood glucose levels by insulin and glucagon in fed and fasting states.

Thyroid hormone effects on the pancreatic β -cell

Several studies have shown links between TH action and pancreatic β -cell development and function [14,15]. Neonatal β -cells have thyroid hormone receptors (THRs). Aguayo-Mazucato et al. [14] have described the role of TH and THRs in postnatal rat pancreatic β -cell development. Specifically, triiodothyronine (T3) stimulates β -cell proliferation from birth through the first week of life. THR also has a direct receptor-ligand interaction with the MAF bZIP transcription factor A (MAFA) promoter. In addition, T3 increases glucose-stimulated insulin secretion *in vitro*. *In vivo*, T3 administration acts on a pro-survival, anti-apoptotic factor for β -cells and improves glucose intolerance in streptozotocin-induced diabetic mice [15].

Peripheral effects of thyroid hormone on insulin secretion and resistance

TH impacts insulin secretion and glucose uptake via differing effects in the gastrointestinal tract, liver, skeletal muscles, and adipose tissue. TH enhances glucose absorption by increasing gastrointestinal motility [16]. In liver, it increases hepatic glucose output through increased hepatic expression of glucose

transporter 2 (GLUT2) which stimulates the endogenous production of glucose through an increase in gluconeogenesis and glycogenolysis. T3 also increases hepatic gluconeogenesis by increasing activity of phosphoenolpyruvate carboxykinase (PEPCK), an enzyme that enhances gluconeogenesis [17,18]. Furthermore, stimulated glycogenolysis and gluconeogenesis induces hyperinsulinemia and glucose intolerance, resulting in peripheral insulin resistance [16]. In adipose tissue, TH increases lipolysis, resulting in an increase in free fatty acid that stimulates hepatic gluconeogenesis [19]. TH also directly stimulates insulin secretion by pancreatic β -cells and increases glucagon release by pancreatic α -cells [16]. Hyperthyroidism increases glucose transporter type 4 (GLUT4) gene expression and glucose uptake in skeletal muscles [16].

Central interactions of thyroid hormones on glucose and lipid regulation

T3 can centrally modulate glucose production through a sympathetic pathway from the hypothalamic paraventricular nucleus (PVN) to liver. T3 in the hypothalamic PVN increases hepatic glucose production, independent of glucoregulatory hormones [20].

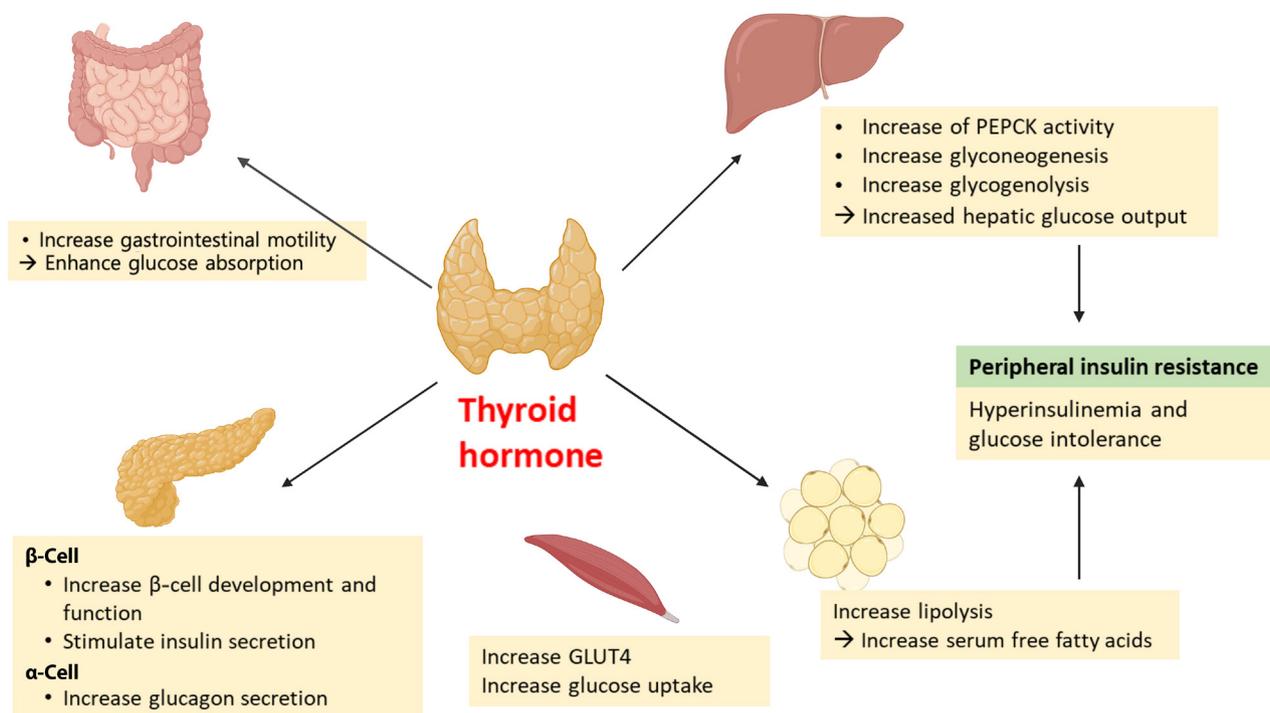


Fig. 2. Effects of thyroid hormone on glucose metabolism. GLUT4, glucose transporter type 4; PEPCK, phosphoenolpyruvate carboxykinase.

THYROID DISORDERS AND DIABETES MELLITUS

Thyroid disorders and DM are closely linked. Many studies have demonstrated the higher prevalence of thyroid dysfunction in both T1DM and T2DM. The prevalence of thyroid disorders in a patient with DM is variable among the population studied. A large clinical study of 1,310 adult patients with diabetes reported a 13.4% overall prevalence of thyroid diseases. The prevalence was 31.4% in T1DM and 6.9% in T2DM, and 8.8% in men and 16.8% in women [21]. A meta-analysis of all available data in 10,920 patients with DM revealed an 11% prevalence of thyroid diseases. In this study, there was no difference between T1DM and T2DM, but the prevalence in women was more than twofold than that in men [22]. The fact that thyroid disorders increase the risk of DM has been reported in nationwide Danish health register study as follows. In an observational cohort study of 2,631 hyperthyroid singletons and 375 twin pairs discordant for hyperthyroidism, hyperthyroid individuals were 43% more likely to be diagnosed with DM [4]. In separate observational cohort study of 2,822 individuals with hypothyroidism, the group with hypothyroidism had a 40% higher prevalence of DM compared to controls [6].

Thyroid disorders and T1DM

Association of AITD and T1DM

T1DM accounts for 5% to 10% of diabetes cases and stems from cell-mediated autoimmune destruction of pancreatic β -cells [23]. Related autoimmune markers include autoantibodies to insulin, glutamic acid decarboxylase 65 (GAD65), the tyrosine phosphatase-related islet antigen-2 (IA-2) and IA-2b, and zinc transporter 8 (ZnT8). Patients with T1DM are also at increased risk for development of other autoimmune disorders, such as: Hashimoto thyroiditis, Graves' disease, celiac disease, Addison disease, autoimmune hepatitis, vitiligo, myasthenia gravis, and pernicious anemia [1]. AITD and T1DM are related target-organ autoimmune diseases with AITD being noted in 17% to 30% of adults with T1DM and with increased risk being observed in both autoimmune hypothyroidism and hyperthyroidism [24]. This association is linked to the expression of thyroid autoantibodies like thyroid peroxidase antibody (TPO Ab) and thyroglobulin antibody (TG Ab) [25,26]. A study that evaluated the prevalence of various autoantibodies in a population of 814 individuals with T1DM revealed that TPO Ab and Tg Ab were the most common autoantibodies

with a proportion of 29% [27].

There is significant evidence for a genetic association between the two diseases [28]. These two diseases frequently occur within the same family and even within the same individual. AITD and T1DM often occur in the same individual or more than one member of the same family, as the phenotype classified as one of the autoimmune polyglandular syndrome 3 variant (APS3), especially APS type 3A [29,30]. Both T1DM and AITD are multifactorial autoimmune endocrine diseases with several susceptibility genes and environmental factors contributing to disease etiology. The human leukocyte antigen (HLA) class II, cytotoxic T lymphocyte antigen-4 (CTLA-4) (on chromosome 2q33), protein tyrosine phosphatase non-receptor type 22 (PTPN22) (1p13), forkhead box P3 (FOXP3) (Xp 11), and interleukin 2 receptor α (IL-2R α) (10p15) are major genes found to contribute to a joint susceptibility for T1DM and AITD [29,31,32]. These genes are immunologically linked, influencing T cell activity. The HLA-DR molecules present autoantigens to T cells, and CTLA-4 is expressed on T cells and acts as a costimulatory receptor which downregulates T cells. PTPN22 is a negative regulator of T cell receptor signaling pathway, and FOXP3 regulates the differentiation of regulatory T cells, while IL-2R α actively suppresses autoreactive T cells via CD25 (α chain of the high-affinity IL-2 receptor) [29,32].

Screening recommendation for thyroid dysfunctions in patients with T1DM

Thyroid dysfunction is especially common in T1DM, particularly those with positive TPO Abs [25]. In these patients, thyroid diseases may be asymptomatic or the symptoms may be masked by symptoms related to poor diabetic control. Thus, a symptom-based approach to thyroid disease can miss the diagnosis in T1DM. Routine screening may help detect thyroid disease in such scenarios. Currently, screening for thyroid dysfunction is recommended in children, adolescents, and adults with T1DM by the American Thyroid Association (ATA) [33], the British Thyroid Association (BTA) [34], the American Diabetes Association (ADA) [35], the American Association of Clinical Endocrinologist (AACE) [36], National Institute for Health and Care Excellence (NICE) [37], and the International Society for Pediatric and Adolescent Diabetes (ISPAD) [38] but not by the United States Preventive Service Task Force (USPSTF) (Table 1) [39].

Table 1. Recommendations for thyroid hormone screening in patient with T1DM

Guideline	Screening recommendation	Comments
2010 Guideline of the ATA for detection of thyroid dysfunction [33]	Patients with diabetes may require more frequent TSH monitoring.	Recommend TSH beginning at age 35 years and every 5 years thereafter, with more frequent monitoring if high risk factors such as diabetes.
BTA, the UK guidelines for the use of thyroid function tests, 2006 [34]	Annually	They note a high frequency of asymptomatic thyroid dysfunction in patients with T1DM and that screening is cost-effective.
ADA, standards of medical care in diabetes, 2008 [35]	Screen for TPO Ab and Tg Ab at diagnosis Check TSH after metabolic control established. If normal, recheck every 1–2 years, or sooner if signs/symptoms. Check FT4 if TSH is abnormal.	
AACE, medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism, 2002 [36]	Examine for goiter. Check TSH regularly, especially if a goiter develops or if evidence is found of other autoimmune disorders.	They note that approximately 10% of patients with T1DM will develop chronic thyroiditis +/- subclinical hypothyroidism.
NICE guideline for type 1 diabetes in adults: diagnosis and management, 2015 [37]	Annually	
ISPAD, 2018 [38]	Check TSH and TPO Abs at diagnosis. If normal and asymptomatic, screen every other year.	
2015 Recommendation statement of USPSTF: screening for thyroid dysfunction [39]	No specific recommendation	They conclude that the current evidence is insufficient to recommend screening for thyroid dysfunction in non-pregnant, asymptomatic adults.

T1DM, type 1 diabetes mellitus; ATA, American Thyroid Association; TSH, thyroid-stimulating hormone (thyrotropin); BTA, British Thyroid Association; UK, United Kingdom; ADA, American Diabetes Association; TPO Ab, thyroid peroxidase antibody; Tg Ab, thyroglobulin antibody; FT4, free thyroxine; AACE, American Association of Clinical Endocrinologist; NICE, National Institute for Health and Care Excellence; ISPAD, International Society for Pediatric and Adolescent Diabetes guidelines; USPSTF, United States Preventive Service Task Force.

Thyroid disorders and T2DM

Thyroid disorders and insulin resistance

The glucose homeostasis disorder, insulin resistance, is defined as the decreased metabolic response to insulin in the peripheral tissues such as muscle, liver, and adipose [40]. To maintain glucose homeostasis, pancreatic β -cells compensate for insulin resistance by augmenting insulin secretion, leading to a state of chronic hyperinsulinemia. Insulin resistance plays a role in the pathogenesis of T2DM. Thyroid function is associated with insulin resistance not only in clinically diagnosed DM but also in subjects with a normal glucose tolerance [41,42]. Both hyperthyroidism and hypothyroidism can affect insulin resistance, although by different mechanisms.

Thyrotoxicosis and T2DM

The prevalence of hyperthyroidism is higher in patients with

diabetes than in the general population. Approximately 4.4% of adults with T2DM also had hyperthyroidism compared to an average of 1.3% in the general United States population [2,21]. Thyrotoxicosis has been recognized to lead to hyperglycemia via several mechanism [43]. Excess TH can increase glucose absorption by the gastrointestinal tract, glucose production in the liver via increasing gluconeogenesis and glycogenolysis, and the concentration of free fatty acids via promoting lipolysis [16]. TH stimulates insulin secretion and induces hyperinsulinemia, although thyrotoxicosis also accelerates insulin degradation and decreases the half-life of insulin [44]. Furthermore, the increased hepatic glucose output induces hyperinsulinemia, glucose intolerance, and peripheral insulin resistance. Thus, hyperthyroidism precipitates impaired fasting glucose and/or diabetes and worsens glycemic control in pre-existing T2DM. Moreover, thyrotoxicosis may rarely precipi-

tate diabetic ketoacidosis not only in patients with T1DM, but also in patients with T2DM when accompanied by insulin deficiency which can enhance the risk for lipolysis [16,45,46].

Hypothyroidism and T2DM

The prevalence of hypothyroidism is higher in patients with diabetes than in the general population. The prevalence of hypothyroidism in T2DM has been reported to be between 5.7% and 25.3% [47-49]. These wide range could be explained by differences in age, sex, and the degree of iodine intake of the populations surveyed [50]. The prevalence of hypothyroidism increased in older age, female gender, with family history of thyroid disease and positive TPO Ab [51].

Hypothyroidism is associated with insulin resistance and glucose intolerance with treatment of hypothyroidism and a return to a euthyroid states being associated with improved insulin sensitivity [41,52,53]. The pathogenesis of insulin resistance in a hypothyroid state is different from that seen with thyrotoxicosis. Hypothyroidism results in impaired glucose absorption from the gastrointestinal tract, delayed peripheral glucose assimilation, and gluconeogenesis [41]. Insulin resistance is thought to be associated with decreased glucose disposal, a result of decreased skeletal muscle and adipose tissue sensitivity to insulin [54,55]. This deterioration of glucose metabolism is also seen in subclinical hypothyroidism. One meta-analysis study revealed that the risk of developing subclinical hypothyroidism increased by 1.93-fold in T2DM patients compared to non-diabetics and that subclinical hypothyroidism may also be associated with an increase in diabetic complications [56]. Free thyroxine (T4) levels in the lower end of reference range are also associated with higher glycosylated hemoglobin (HbA1c) levels in euthyroid state [57].

Screening recommendation for thyroid dysfunction in patients with T2DM

Contrary to the guideline for T1DM, there is a lack of recommendations for screening for thyroid disease in patients with T2DM. The ATA recommended that adults who are at least 35 years old should be screened for thyroid disorders by measuring a thyroid-stimulating hormone (TSH) concentration and then every 5 years in the 2010 guidelines. Although there is no mention of DM type, the guideline recommends more frequent tests in those with high risk factors like diabetes [33]. The United Kingdom 2006 guidelines recommended a thyroid function test at the time of diagnosis for patients with T2DM but not an-

nual testing [34]. Conversely, USPSTF reports that there is insufficient evidence to recommend thyroid dysfunction screening in non-pregnant or asymptomatic adults in 2015 [39]. There is no mention of monitoring thyroid function in T2DM in the 2015 NICE guidelines [58], the ADA guideline [59], the ATA/AACE guideline [60], and the ISPAD guideline (Table 2) [61,62]. Therefore, the necessity of a screening for thyroid dysfunction in patients with T2DM is debated at this time.

Thyroid disorders in pregnant women with diabetes Changes in thyroid function during pregnancy and effect on glucose homeostasis

During pregnancy, numerous hormonal and metabolic changes occur, which affect glucose metabolism and thyroid function [63]. In a normal pregnancy, a 50% to 60% decrease in insulin sensitivity occurs in both pregnant women with normal glucose tolerance and women with gestational diabetes. In women with normal glucose tolerance, the decrease of insulin sensitivity is overcome by increased insulin secretion from pancreatic β -cells, whereas gestational diabetes occurs when insulin secretion is not sufficient to match this higher demand [64].

During pregnancy, the maternal thyroid gland increases in size by 10% in iodine replete countries but by 20% to 40% in iodine deficient countries [65]. Production of THs, T4, and T3 increases by almost 50% and for this reason, iodine daily intake should also be increased by 50%. The World Health Organization recommends daily iodine intake of 250 μ g for pregnant and lactating women [66]. In early pregnancy, the placenta makes human chorionic gonadotropin (hCG) which is a member of the glycoprotein hormone family that is composed of common α -subunits and a hormone-specific β -subunits. The hCG α -subunit sequence is identical to the sequences of the α -subunits of TSH, follicle-stimulating hormone and luteinizing hormone [67]. Increased hCG concentration during the first trimester of pregnancy stimulates the thyroid gland thereby increasing production and release of THs resulting in decrease of TSH [66]. Hyperemesis gravidarum is extreme, persistent nausea and vomiting during pregnancy which can lead to dehydration, weight loss of at least 5% from pre-pregnancy baseline, ketonuria, and electrolyte imbalances. The exact cause is not fully understood, but it is believed to be caused by a rapid rising blood level of hCG [68,69]. hCG is a thyroid stimulator and most transient non-immune hyperthyroidism in early pregnancy is related to increased hCG levels while rare

Table 2. Recommendations for thyroid hormone screening in patients with T2DM

Guideline	Screening recommendation	Comments
2010 Guideline of the ATA for detection of thyroid dysfunction [33]	Patients with diabetes may require more frequent TSH measurement.	Recommend TSH beginning at age 35 years and every 5 years thereafter, with more frequent monitoring if high risk factors such as diabetes (does not distinguish between T1DM and T2DM)
BTA, the UK guidelines for the use of thyroid function tests, 2006 [34]	Check TSH at diagnosis.	They do not recommend routine annual screening.
2015 Recommendation statement of USPSTF: screening for thyroid dysfunction [39]	No specific recommendation	They conclude that the current evidence is insufficient to recommend screening for thyroid dysfunction in non-pregnant, asymptomatic adults.
NICE guideline for type 2 diabetes in adults: management, 2015 [58]	No specific recommendation	
ADA, guideline 2018 [59]	No specific recommendation	
ATA/AACE, clinical practice guidelines for hypothyroidism in adults, 2012 [60]	No specific recommendation	
ISPAD, 2009 [61,62]	No specific recommendation	

T2DM, type 2 diabetes mellitus; ATA, American Thyroid Association; TSH, thyroid-stimulating hormone (thyrotropin); T1DM, type 1 diabetes mellitus; BTA, British Thyroid Association; UK, United Kingdom; USPSTF, United States Preventive Service Task Force; NICE, National Institute for Health and Care Excellence; ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologist; ISPAD, International Society for Pediatric and Adolescent Diabetes guidelines.

cases of familial recurrent gestational hyperthyroidism are caused by a mutant thyrotropin receptor that is hypersensitive to hCG as has been reported with even normal range serum hCG [70].

Thyroid dysfunction and DM are the common endocrinopathies during pregnancy and can affect both maternal and fetal health [71,72]. Thyroid function abnormalities are more common in pregnant women in the first trimester [73] with hypothyroidism, hyperthyroidism, and thyroid autoimmunity being common conditions in pregnancy, with prevalence rates of 2%–3%, 0.1%–0.4%, and up to 17% [74–76]. A higher prevalence of hypothyroidism in women with gestational diabetes mellitus (GDM) has been reported [77] and this association is also seen in postpartum thyroiditis (PPT), which is an autoimmune-mediated destructive thyroiditis in the 1st year postpartum. According to the studies, PPT is also three to four times more common in women with T1DM than in healthy women [78–80].

Considering that THs affect glucose homeostasis, thyroid disorders have been thought to affect the development of gestational diabetes or glucose control of pregnant women with diabetes. Pregnant women with either overt hypothyroidism or subclinical hypothyroidism have an increased risk of GDM [77,81]. There are also reports that maternal isolated hypothy-

roxinaemia (normal TSH concentration in conjunction with a low free T4) is associated with adverse metabolic parameters including increased maternal body mass index, higher fasting and postprandial glucose, higher HbA1c, higher triglycerides and increased insulin resistance (homeostasis model assessment of insulin resistance) in pregnancy [82,83]. Recently, there is a report that higher free T3 levels in early pregnancy may correlate with a greater risk for GDM developing compared to women who have normal levels of this hormone [84].

Screening recommendation for thyroid dysfunction in pregnant patients

Untreated overt hypothyroidism and hyperthyroidism are associated with adverse obstetrical and fetal outcomes such as spontaneous abortion, preeclampsia, preterm birth, abruptio placentae, poor fetal growth, and stillbirth [85,86]. Subclinical hypothyroidism has been related to adverse obstetrical outcomes such as abruptio placentae, preterm birth, and impaired neurodevelopment in offspring [87,88]. However, detection and treatment of maternal subclinical hypothyroidism has also not been shown to cause improved pregnancy outcome and neurocognitive function in offspring [89,90]. Therefore, clinical guidelines do not recommend universal thyroid function screening in pregnant women, but instead limited to women

who have signs and symptoms of possible thyroid dysfunction and high-risk groups including those with T1DM or family history of thyroid disease. Similarly, screening for thyroid dysfunction is recommended in pregnant women with T1DM by the ATA [66], the BTA [34], the Endocrine Society [91], the AACE [60], the Korean Thyroid Association (KTA) [92], and the American College of Obstetricians and Gynecologists

(ACOG) (Table 3) [93].

ANTIDIABETIC AGENTS AND THYROID DISORDERS

The use of certain antidiabetic drugs in patients with T2DM may influence thyroid function. We explore common oral an-

Table 3. Recommendations for thyroid hormone screening in pregnant diabetic patients

Guideline	Screening recommendation	Comment
2017 Guidelines of the ATA for the diagnosis and management of thyroid disease during pregnancy and the postpartum [66]	Check TSH in pregnant women with T1DM or other autoimmune disorders.	They do not recommend universal screening for patients who are pregnant or are planning pregnancy. Screening is recommended if one of the following risk factors: (1) A history of or current symptoms/signs of thyroid dysfunction, (2) thyroid antibody positivity or goiter, (3) prior head and neck radiation or thyroid surgery, (4) age > 30 years, (5) T1DM or other autoimmune disorders, (6) prior pregnancy loss, preterm delivery, or infertility, (7) prior pregnancies (≥ 2), (8) family history of AITD or thyroid dysfunction, (9) morbid obesity (BMI ≥ 40 kg/m ²), (10) use of amiodarone or lithium, or recent administration of iodinated radiologic contrast, (11) residing in an area of known iodine insufficiency.
BTA, 2006 UK guidelines for the use of thyroid function test [34]	Check TSH, FT4, and TPO Abs in women with T1DM prior to conception. Monitor thyroid function during pregnancy and 3 months post-partum.	They note that women with T1DM are three times more likely to develop post-partum thyroid dysfunction.
2014 Endocrine Society Recommendation [91]	Check TSH in pregnant women with T1DM.	T1DM is considered a significant risk factor as are: current thyroid therapy, family history of AITD, goiter, history of autoimmune disorder, high-dose neck radiation, postpartum thyroid dysfunction, and previous delivery of infant with thyroid disease.
ATA/AACE, clinical practice guidelines for hypothyroidism in adults, 2012 [60]		They do not recommend universal screening for patients who are pregnant or are planning pregnancy.
2014 KTA guideline for the diagnosis and management of thyroid disease during pregnancy and postpartum [92]	Check TSH in pregnant women with T1DM.	They recommend screening early in pregnancy in the setting of T1DM or if other high risk factors.
ACOG practice bulletin, clinical management guideline for obstetrician-gynecologists: thyroid disease in pregnancy [93]	Check TSH in pregnant women with T1DM.	They do not recommend universal screening for thyroid disease in pregnancy. Indications include personal or family history of thyroid disease, T1DM, or clinical suspicion of thyroid disease.

ATA, American Thyroid Association; TSH, thyroid-stimulating hormone (thyrotropin); T1DM, type 1 diabetes mellitus; AITD, autoimmune thyroid disease; BMI, body mass index; BTA, British Thyroid Association; UK, United Kingdom; FT4, free thyroxine; TPO Ab, thyroid peroxidase antibody; AACE, American Association of Clinical Endocrinologist; KTA, Korean Thyroid Association; ACOG, American College of Obstetricians and Gynecologists.

tidiabetic agents and their impact on TH levels here (Table 4).

Metformin

Metformin is a widely used oral antidiabetic drug for treatment of T2DM. Metformin suppresses hepatic gluconeogenesis via stimulating adenosine monophosphate-activated kinase (AMPK) in the liver, but has the opposite effect inhibiting AMPK in the hypothalamus [94]. Metformin has been shown to cross the blood-brain barrier and its concentrations in the hypothalamus match those in plasma in rat experiments, and substantially metformin levels in the pituitary gland increase as well [95]. These effects may fit with some clinical results, indicating that metformin may inhibit pituitary TSH secretion. It was first reported that metformin therapy decreases serum TSH levels in patients with T2DM with primary hypothyroidism in 2006 [96]. Several studies have shown that metformin administration in diabetic patients with primary hypothyroidism is associated with a reduction in serum TSH levels and this effect was observed in both patients under TH replacement therapy and in untreated patients [97,98]. The TSH-lowering effect of metformin was observed in patients with overt hypothyroidism and subclinical hypothyroidism, but not in euthy-

roid patients [98,99]. Despite the reduction in TSH, there is no change in [96] and plasma free T4 and free T3 concentrations, and the effect was not associated with clinical hyperthyroidism. In addition, this effect was reversible and usually resolved by 3 months after discontinuation [97,98].

Metformin has been shown to have beneficial effects in various types of cancers such as colon, rectum, pancreas, breast and prostate cancer [100]. Metformin inhibits the mammalian target of rapamycin (mTOR) activity by activating liver kinase B1 (LKB1) and AMPK, and thus prevents protein synthesis and cell growth. Metformin also can activate p53 by activating AMPK and thereby ultimately stop the cell cycle [101,102]. One study showed that metformin significantly decreased thyroid nodule size by 30%–50% in patients with insulin resistance [103]. Studies on the anti-tumor effect of metformin in thyroid cancer have been conducted, and some studies have reported that metformin inhibits thyroid cancer cell growth and induces cell-cycle arrest and apoptosis through AMPK activation and mTOR inhibition *in vivo* and *in vitro* [104–107]. A retrospective cohort study of 128,453 Korean adult diabetic patients reported that thyroid cancer decreased significantly in metformin users compared to metformin nonusers [108]. These find-

Table 4. Effects of antidiabetic agents on thyroid disorders

Metformin	Metformin administration in diabetic patients is associated with a reduction in serum TSH levels without change of plasma FT4 and FT3 concentration. TSH level monitoring may be necessary after the use of metformin in diabetic patients with overt and subclinical hypothyroidism. Metformin may reduce thyroid nodule size and reduce thyroid cancer cell growth.
Sulfonylureas	Hypothyroidism occurred more frequently in diabetic patients taking first-generation sulfonylurea. The second-generation sulfonylurea, glibenclamide and gliclazide have little influence on thyroid hormone metabolism.
Thiazolidinediones	TZDs may exacerbate TED. TZDs should be used carefully in patients with T2DM with clinically active TED.
Incretin mimetics	GLP-1RAs increase medullary thyroid cancer in rats, but not in monkeys and humans. Monitoring for the occurrence of MTC in patients taking GLP-1RAs is not recommended. Use of GLP-1RAs in patients with a personal or family history of MTC or MEN type 2 is not recommended.
Colesevelam	BASs can sequester T4 in the intestine and increase its fecal excretion, thus, restricting the enterohepatic reabsorption into the systemic circulation. Colesevelam binds levothyroxine and decreases its absorption. Caution may be required when using colesevelam and levothyroxine together.

TSH, thyroid-stimulating hormone (thyrotropin); FT4, free thyroxine; FT3, free triiodothyronine; TZD, thiazolidinedione; TED, thyroid eye disease; T2DM, type 2 diabetes mellitus; GLP-1RA, glucagon-like peptide-1 receptor agonist; MTC, medullary thyroid cancer; MEN, multiple endocrine neoplasia; T4, thyroxine.

ings suggest that metformin could be of potential benefit in thyroid cancer, especially in diabetic patients, but additional studies are required.

Sulfonylureas

Sulfonylurea drugs have been used in the treatment of T2DM since 1950's. These drugs have been reported to have both anti-thyroid and goitrogenic activity. Early studies showed that large doses of sulfonylureas increase the weight of the thyroid gland and reduced iodine content and fixation of radioiodine uptake in animal models [109,110]. It has been reported that hypothyroidism occurs more frequently in diabetic patients taking first-generation sulfonylureas than in patients treated with diet alone or insulin [111]. However, studies on the second-generation sulfonylureas, glibenclamide, and gliclazide have shown that the use of these agents appear to have no influence on TH metabolism [112,113].

Thiazolidinediones

Thiazolidinediones (TZDs) are an important class of insulin sensitizers used in the treatment of T2DM. TZDs were known to act by increasing the transactivation activity of peroxisome proliferator-activated receptors (PPARs). TZDs are agonists of PPAR- γ , can reduce hepatic glucose production, increase peripheral glucose utilization and lipid metabolism [114]. PPAR- γ is found predominantly in adipose tissue and plays a dominant role in adipocyte differentiation [115]. PPAR- γ is also strongly expressed in thyroid tissue of patients with thyroiditis and Graves' disease and in the orbital tissue of patients with thyroid eye disease (TED) [116]. TED is characterized by swelling of extraocular muscles and an extension of adipose tissue volume within the confines of the bony orbit [117]. TSH receptor expression in TED orbital preadipocyte fibroblasts is linked to adipogenesis, and stimulation of the PPAR- γ receptor results in differentiation of these cells. Rosiglitazone treatment of orbital preadipocyte fibroblasts from patients with TED revealed stimulation of both adipocyte differentiation and TSH-dependent cyclic adenosine monophosphate production in these cells [117]. In some patients with T2DM, it has been reported that eye protrusion can worsen while taking TZDs [118,119]. Thus, TZDs should be used carefully in patients with T2DM with clinically active TED.

The result from one study suggests that rosiglitazone administration in T2DM may reduce the risk of thyroid cancer [120]. The relationship between TZDs and thyroid cancer, however,

has not been clearly elucidated.

Incretin mimetics: GLP-1 receptor agonists and dipeptidyl peptidase-4 inhibitors

Incretin mimetics are agents that act like or increase endogenous incretin hormones, including glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase 4 (DPP4) inhibitors, respectively. GLP-1R agonists have shown association with C-cell proliferation and potential for increased risk of medullary thyroid cancer (MTC) in preclinical studies in rats [121-123]. Long-term dosing with liraglutide causes C-cell hyperplasia, calcitonin production in a dose dependent manner, and tumor formation in rodents [121-123]. This effect, however, was not seen in monkeys and humans. Prolonged use of liraglutide at very high doses did not produce C-cell proliferation in monkeys and did not induce significant calcitonin level changes in human clinical studies [124,125]. Exenatide also did not increase calcitonin in follow-up [126]. Similarly, in the Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER) Trial, liraglutide did not increase calcitonin or cause C-cell malignancies [127]. This may be due to C-cells in monkeys and humans having lower expression of GLP-1R and decreased responsiveness to GLP-1R agonists compared to rodents [125]. The Food and Drug Administration (FDA) does not recommend monitoring for the occurrence of MTC in patients taking GLP-1R agonists; however, the use of GLP-1R agonists in patients with a personal or family history of MTC or multiple endocrine neoplasia (MEN) type 2 is not recommended.

The relationship between DPP4 inhibitors and thyroid cancer has not been well reported. One study with sitagliptin among Taiwanese T2DM patients showed an increased prevalence of thyroid cancer. This was during the first year of treatment; however, and the impact of DPP4 inhibitor to this finding is thought to not necessarily be directly related given this short time interval and lack of additional supportive data [128].

Incretin mimetics have been shown to alter TSH concentration; however, this does not appear to be clinically significant. The GLP-1R agonist, exenatide, decreased TSH concentrations in diabetics after 6 months. Levels remained in the detectable range, and there were no significant changes in free T4, free T3, or thyroid volume [126]. A small study reported that diabetics followed for over three years taking a DPP4 inhibitor compared to diabetics on alternative therapy had higher TSH

concentrations. TSH was still within the normal range and free T4 concentration was not significantly different between the two groups [129]. Larger, longer-term studies are warranted.

Colesevelam

Bile acid sequestrants (BASs) were developed as lipid-lowering agents for the treatment of hypercholesterolemia and include cholestyramine, colesevelam, colestilan, colestimide, and colestipol. BASs significantly reduce low-density lipoprotein cholesterol levels and improve cardiovascular outcomes in a population of asymptomatic middle-aged men with primary hypercholesterolemia [130]. BASs also lower glucose levels in patients with T2DM [131-134]. Among BAS, colesevelam was approved in 2008 by the U.S. FDA to improve glycemic control in adults T2DM patients [135]. TH including T4 and T3 are secreted into the bile. BASs can sequester T4 in the intestine and increase its fecal excretion, thus, restricting the enterohepatic reabsorption into the systemic circulation. Cholestyramine for example, is used for the treatment of thyrotoxicosis including thyroid storm because of this effect [136]. BAS agents can enhance the clearance of THs and may reduce the blood levels and effects of levothyroxine by interfering with the absorption of the drug. Cholestyramine and colestipol, inhibit absorption of levothyroxine through the binding of T4 to the basic anion copolymer resins in the gastrointestinal tract. Colesevelam is a nonabsorbed polymer that binds to bile acids in the small intestine, thereby preventing their reabsorption. Although it has been proposed that the binding of colesevelam to other drugs should be less problematic than that seen with the older BASs, it is probable that it too binds levothyroxine and decreases its absorption [137]. Therefore, caution should be taken when using colesevelam and levothyroxine together.

Other agents

Limited data are available on the potential impact of acarbose on thyroid function and thyroid cancer risk/benefit. Acarbose increased levels of TH in dexamethasone-induced hyperglycemic mice, although the mechanism of this is not well understood [138]. In a retrospective study, acarbose was associated with lower rate of papillary thyroid carcinoma growth [139].

Similarly, limited data exist on the impact of sodium glucose transporter type 2 (SGLT2) inhibitors and TH. In animal models SGLT2 inhibitors have been theorized to potentially increase risk of MTC; however, this has not been shown in humans [140,141].

THYROID DISORDERS AND HYPOGLYCEMIA

Glucose is an essential energy resource for the survival and activity of the brain. As the brain is unable to store glucose itself, it is very important that adequate plasma glucose levels be maintained and available to the brain at all times. There are several protective mechanisms to prevent or remediate hypoglycemia. A decrease in insulin secretion and activation of the counterregulatory response are the main response mechanisms for avoidance or correction of hypoglycemia. Counterregulatory hormones that act to prevent hypoglycemia include: glucagon, epinephrine, GH, cortisol, and neurotransmitters [142]. Hypoglycemia is common in T1DM and T2DM, in patients using insulin or some oral hypoglycemia agents. Hypothyroidism is one of the most common endocrine disorders, and frequently coexists with T1DM or T2DM [25,143]. Hypothyroidism may contribute to hypoglycemia via affecting various hormones and nervous function. In secondary hypothyroidism caused by hypopituitarism, hypoglycemia may be induced by adrenocorticotrophic hormone and GH deficiency, but the risk of hypoglycemia is also increased in patients with primary hypothyroidism. TH affects hypothalamic-pituitary-adrenal (HPA) function and reduces GH and cortisol secretion, thereby interfering with the appropriate counterregulatory response to insulin induced hypoglycemia. Primary hypothyroidism reduces basal and stimulated GH, by acting on both the hypothalamus and pituitary [144]. In addition, hypothyroid patients may have co-existing relative adrenal insufficiency, thus weakening HPA response to hypoglycemia [145]. Hypothyroidism also affects glucose homeostasis, and these changes may be related to hypoglycemia. In hypothyroid patients, gluconeogenesis is reduced in skeletal muscle and in adipose tissue [146] and glycogenolysis is impaired [147]. These changes induce a delayed recovery from hypoglycemia. There are also reports that hypothyroidism may contribute to hypoglycemia through mechanisms including potentially impaired glucagon response and slowed gastric emptying [148,149].

CONCLUSIONS

TH affects glucose homeostasis, and thyroid disorders and DM are associated with each other. Autoimmunity is an important element in the relationship between T1DM and AITD. Thyroid dysfunction, both hyperthyroidism and hypothyroidism,

is associated with insulin resistance and T2DM. Hypothyroidism can also increase risk of hypoglycemia in some setting. The association between TH and DM is also seen in pregnant women with gestational or pre-existing T1DM or T2DM. Screening for thyroid dysfunction is usually recommended in patients with T1DM, but there is a lack of recommendations in the screening for thyroid disease in patient with T2DM. Moreover, most guidelines do not recommend universal thyroid function screening in pregnant women, but instead limited to high-risk groups including T1DM. The use of certain antidiabetic agents influences thyroid function, TED, and thyroid cancer risk. Therefore, caution is required not only in interpreting TH levels when using these drugs in patients with T2DM, but also in using the drugs in patients with TED or risk of thyroid cancer. In conclusion, future research is warranted to further investigate the connections between DM and thyroid disorders and clinicians should take special consideration when evaluation patients with these conditions.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Young Sil Eom <https://orcid.org/0000-0002-9281-7290>

Victor J. Bernet <https://orcid.org/0000-0002-2477-5631>

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