ATATURK UNIVERSITY PUBLICATIONS

Review

DOI: 10.5152/Pharmata.2023.23009

The Relationship Between Euthyroid, Hyperthyroid, Hypothyroid, and Type 2 Diabetes

Zerrin KUTLU
Afra Dilay KAMACI

Department of Biochemistry, Faculty of Pharmacy, Atatürk University, Erzurum, Turkey

ABSTRACT

Diabetes mellitus (DM) and thyroid dysfunction, which have a significant incidence worldwide, are the most common endocrine system disorders that occur together in patients. Our aim is to explain these 2 diseases with high incidence and the relationship between these 2 diseases. Thyroid hormones (TH) are essential hormones that govern body metabolism. Thyroid hormone changes are thought to be effective on the pathogenesis of DM. Diabetes mellitus treatments can be beneficial, as TH changes may contribute to the pathogenesis of DM. However, more research needs to be done. This lack of information limits potential biomarkers and targets for diagnosis, prognosis, and the development of new DM treatments. The limitations of the use of natural THs have led to the development of synthetic hormones called thyromimetics. However, most of the thyromimetics tested so far have been ineffective or toxic.

Keywords: Diabetes, euthyroid, hyperthyroid, hypothyroid

INTRODUCTION

Diabetes mellitus (DM) is a significant global health issue that has a profound impact on the quality of life of affected individuals. The prevalence of diabetes is increasing worldwide, and it is projected to continue to rise in the coming years. According to the International Diabetes Federation (IDF), the number of adults with diabetes was estimated to be 1 in 11 in 2015, and this number is expected to reach 642 million by 2040. Furthermore, diabetes-related mortality is a major concern. The IDF reported that in 2019, approximately 4.2 million deaths were attributed to diabetes. Without effective intervention and management, this number is projected to increase to 700 million by 2045. Diabetes is among the top 10 causes of death globally, highlighting the severity of the disease and its associated complications.[1]

Diabetes mellitus is indeed a rapidly growing disease worldwide, characterized by chronic elevated blood sugar levels. It is an endocrine system disorder that disrupts the metabolism of carbohydrates, fats, and proteins due to insufficient insulin secretion or reduced tissue sensitivity to insulin. Insulin, which is produced by the beta cells in the pancreas, plays a vital role in regulating blood sugar levels. In individuals with DM, there is a loss of functional beta-cell mass, leading to an imbalance in insulin production and utilization. This results in an inability to effectively regulate blood glucose levels.[2]

Types of Diabetes Mellitus

Today, diabetes is classified in four different ways, and it now includes 4 main categories

- Type 1 diabetes (T1D): This type of diabetes is characterized by autoimmune destruction of the beta cells in the pancreas, resulting in an absolute deficiency of insulin. It often develops early in life, and individuals with T1D require lifelong insulin therapy to manage their blood sugar levels.
- Type 2 diabetes (T2D): Type 2 diabetes is the most common form of diabetes and is usually associated with insulin resistance, where the body's cells become less responsive to insulin. Over time, the beta cells in the pancreas may also progressively lose their ability to produce sufficient insulin. Type 2 diabetes is often associated with lifestyle factors such as obesity, sedentary behavior, and poor dietary habits. It can be managed through lifestyle modifications, oral medications, or insulin therapy.
- Gestational diabetes: Gestational diabetes occurs during pregnancy and is diagnosed in the second or third trimester. It is characterized by elevated blood sugar levels that were not present before pregnancy. Gestational diabetes usually resolves after delivery, but women who have had gestational diabetes have an increased risk of developing T2D later in life.
- Specific types due to other causes: This category includes various forms of diabetes that have specific underlying causes. It encompasses monogenic diabetes syndromes, which are genetic disorders

Received: 03.07.2023
Accepted: 19.09.2023
Publication Date: 09.10.2023

Corresponding Author:
Zerrin KUTLU
E-mail: kutluzerrin@atauni.edu.tr

Cite this article as: Kutlu Z, Kamaci AD. The relationship between euthyroid, hyperthyroid, hypothyroid and type 2 diabetes. *Pharmata* 2023;3(4):105-111.

that affect insulin production or utilization. Exocrine pancreatic diseases, such as pancreatitis or cystic fibrosis, can also lead to diabetes. Additionally, certain medications or chemicals can induce diabetes as a side effect.[3]

The classification of DM into these 4 categories helps guide appropriate treatment strategies and management approaches. It allows healthcare professionals to tailor treatment plans based on the underlying causes and mechanisms of the disease in each individual case.[4]

Epidemiology and Prevalence

Incidence in Children and Adolescents

According to the IDF in 2017, more than 96 000 new cases of T1D are diagnosed each year in children and adolescents under the age of 15. This highlights the significant impact of T1D on the younger population.

Prevalence

Type1 diabetes accounts for approximately 10% of all diabetes cases, as reported by the Diabetes Association of America. It affects around 20 million people worldwide, indicating its global prevalence and impact on individuals living with the condition.

Age of Diagnosis

Although T1D can occur at any age, it is most commonly diagnosed in early childhood (around ages 4 to 5) or during adolescence. This aligns with the observation that T1D is usually diagnosed during critical periods of growth and development.

Increasing Incidence

The incidence of T1D in children under 15 years of age has been observed to increase across Europe. The EURODIAB ACE study group reported an average annual increase of 3.4% in this age group, with the highest increase seen in children under 5 years of age. This suggests a concerning trend of rising T1D cases in younger children.

These statistics emphasize the significant burden of T1D on individuals, families, and healthcare systems globally. Further research and efforts are needed to understand the underlying causes and develop effective strategies for prevention, early diagnosis, and management of T1D.[5]

Pathophysiology

Type 1 diabetes is characterized by an autoimmune response that leads to the selective destruction of insulin-producing pancreatic β-cells. This autoimmune process results in a deficiency of insulin production, leading to high blood sugar levels. The onset of T1D occurs when a significant number of β-cells are destroyed. Type 2 diabetes is primarily characterized by insulin resistance, where the body's cells become less responsive to the effects of insulin. This reduced sensitivity to insulin leads to impaired glucose uptake by cells and elevated blood sugar levels. In addition to insulin resistance, T2D also involves impaired insulin secretion by pancreatic β-cells, contributing to elevated blood glucose levels.

Interaction Between Insulin and the Liver

In normal physiological conditions, insulin plays a crucial role in maintaining appropriate plasma glucose concentrations. One of its functions is to interact with the liver, regulating glucose production and storage. Disruption of this interaction, as seen in T2D, can lead to dysregulated glucose metabolism, impaired insulin secretion, and insulin resistance.

Pathological Defects in T2D

Type 2 diabetes is characterized by a combination of insulin resistance, impaired insulin secretion, and abnormal glucose metabolism. These pathological defects contribute to the development of persistent hyperglycemia and the long-term complications associated with T2D.

Understanding these underlying mechanisms is crucial for developing targeted interventions and treatments for both T1D and T2D. It highlights the importance of insulin production, secretion, and sensitivity in maintaining glucose homeostasis and the need to address these dysfunctions in diabetes management.[5]

Type 1 diabetes is characterized by the autoimmune destruction of pancreatic β-cells, resulting in insulin deficiency. Insulin gene mutations can lead to insulinopathies, causing abnormal insulin synthesis and secretion. Hyperinsulinemia is commonly observed in patients with insulinopathies. In T1D, abnormalities are seen in beta, alpha, and delta cells in pancreatic islets. Insulin secretion defects in T1D include a relative decrease in basal secretion, impaired response to glucose and amino acids, and reduced insulin sensitivity. Type 1 diabetes is also associated with an increase in alpha-cell mass, leading to hyperglucagonemia. Islet amyloid deposits containing islet amyloid polypeptide may play a role in T2D pathogenesis, but its exact role is not fully understood. Type 2 diabetes involves insulin resistance, impaired insulin secretion, and abnormal glucose metabolism. Insulin resistance may result from decreased insulin receptor number, hyperinsulinemia, hyperglycemia, or abnormalities in glucose transporter proteins. Genetic factors, including mutations in the insulin receptor gene and certain glucose transporter genes (GLUT2 and GLUT4), contribute to T2D susceptibility. Environmental factors, such as obesity, sedentary lifestyle, dietary factors, and age, also play a role in insulin resistance. The risk of T2D is influenced by genetic factors, but the individual effects of genetic variants have limited predictive value. Impaired glucose tolerance is characterized by hyperglycemia despite high insulin levels, indicating insulin resistance. As the condition progresses to diabetes, insulin secretion decreases. It is important to note that the information you provided is a general overview, and the development and progression of T1D and T2D involve complex interactions between genetic, environmental, and physiological factors. Further research is needed to fully understand the mechanisms underlying these diseases.[3-5]

Thyroid

The thyroid gland is an endocrine gland responsible for producing and releasing hormones into the bloodstream. The main hormones produced by the thyroid gland are triiodothyronine (T3) and thyroxine (T4). These hormones play a crucial role in regulating metabolism, growth, development, and the functioning of various organs and tissues in the body. The thyroid gland is located in the front of the neck, below the Adam's apple (in men) or the thyroid cartilage. It has a butterfly-shaped structure with 2 lobes connected by a narrow band of tissue called the isthmus. The gland is richly supplied with blood vessels and receives signals from the brain, specifically the hypothalamus and pituitary gland, which help regulate the production and release of thyroid hormones (THs).[6]

Thyroid Physiology

The body needs THs for the metabolism to work correctly and functionally. Thyroid hormone production is a tightly regulated process controlled by a classical negative feedback loop involving

the hypothalamus, pituitary, and thyroid, giving rise to the common name hypothalamus–pituitary–thyroid axis. Thyrotropin-releasing hormone (TRH) is produced in the hypothalamus. After TRH is released, it reaches the pituitary gland and binds to the TRH receptor, stimulating the production and secretion of thyroid-stimulating hormone (TSH), also known as thyrotropin.[6]

In the thyroid, TSH binds to the TSH receptor and induces TH production. Triiodothyronine and T4 are released into the circulation when needed. In the hypothalamus and pituitary, THs act through the nuclear TH receptor β (THRβ) to inhibit TRH and TSH production and secretion, completing a negative feedback loop that maintains physiological levels of TRH, TSH, and THs. In target cells, deiodinases (DIO2 and DIO3) produce T3 from T4 by removing iodine at the 5' position of T4. The expression of different deiodinases is cell type and tissue specific, providing a mechanism to control TH movements independent of circulating TH levels.[7]

Thyroid hormones are essential for the development and maturation of various tissues and for general well-being. In areas of adequate iodine exposure, the prevalence of TH changes in the general population is estimated to be ~0.5%-4%. There are different types of TH changes (hyperthyroidism, subclinical hyperthyroidism, subclinical hypothyroidism, and hypothyroidism) that cause different clinical symptoms. Recent epidemiological meta-analyses have identified a clear association between TH changes and risk of death in the general population.[8]

Thyroid Types

There are thyroid diseases that occur when the homeostasis of the thyroid and thyroid signaling is impaired. These are hypothyroidism, characterized by decreased production and/or circulation of TH; hyperthyroidism, characterized by increased production and/or circulation of TH; and euthyroidism, which is any thyroid enlargement characterized by selective (limited to one or several sites) thyroid tissue enlargement. The onset of these diseases is caused by genetic and environmental factors. Dietary iodine consumption is one of the determinants of thyroid disease risk, but other factors such as aging, gender, genetic predisposition, ethnicity, smoking, endocrine disruptors, and immune system inhibitors also affect the epidemiology of the disease. Between 3% and 10% of adults, especially women, are affected by hypothyroidism. This condition is associated with iodine deficiency, and about a third of the world's population lives in areas with low iodine diets. This is the main cause of hypothyroidism and endemic goiter. In fact, 80% of people living in areas with severe iodine deficiency suffer from goiter. In areas where iodine deficiency is not present, Hashimoto's thyroiditis is the most common type of autoimmune hypothyroidism, occurring in 1% to 2% of cases. The prevalence of hyperthyroidism is 0.8% in Europe and 1.3% in the United States. Marked hyperthyroidism is a disease characterized by low serum TSH concentrations and high levels of serum T4 (tetraiodothyronine), T3, or both. On the other hand, subclinical hyperthyroidism is characterized by low serum TSH but normal serum T4 and T3 levels. As a result of overproduction of T4, diseases such as Graves' disease (GD), thyroid nodules, and thyroiditis occur.[9]

Hashimoto's thyroiditis (HT) is one of the leading autoimmune thyroid diseases (AITD) of hypothyroidism. Approximately 20%-30% of thyroid patients suffer from HT. The cause of the disease is thought to be a combination of genetic predisposition and environmental factors that cause the loss of immunological tolerance. This causes an autoimmune attack on the thyroid tissue and the emergence of the disease. Hashimoto's thyroiditis, which causes chronic inflammation in the thyroid tissue, is the most common of the autoimmune thyroid disorders.[10]

Graves' disease, which occurs as a result of impaired immune tolerance to thyroid antigens, is the most common cause of hyperthyroidism in developed countries. The annual incidence of GD is 20 cases/100 000 people. It is generally seen between the ages of 30 and 60 and is 5 to 10 times more common in women than in men. Genetic predisposition explains 79% of GD risk, and environmental factors explain 21%. Among the endogenous factors of GD, estrogens, X-chromosome inactivation, and microchimerism occupy an important place. Environmental risk factors include smoking, iodine excess, selenium and vitamin D deficiency, and occupational exposure.[11]

Effects of Thyroid Hormones on Glucose and Lipid Metabolism

Thyroid hormones induce catabolism of all types of energy sources by increasing oxygen consumption. Thyroid hormones are effective modulators of lipid and glucose metabolism. Thyroid hormones specifically reduce circulating triglycerides and cholesterol-containing lipoproteins. Thyroid hormones stimulate the expression of sterol response element-binding protein 2 (Srebp-2). Increased Srebp-2 levels contribute to increasing low-density lipoprotein (LDL) receptor expression, which enhances hepatic cholesterol uptake. Moreover, THs are known to increase lipolysis and liponeogenesis simultaneously. In fact, THs are known to increase the expression of carnitine palmitoyltransferase (mitochondrial fatty acid uptake) and acetyl-coenzyme A carboxylase (lipogenic).[12] A comprehensive analysis of these processes has shown that liponeogenesis is enhanced to maintain lipid levels under conditions of elevated lipolysis. Under these conditions, lipolysis is enhanced to provide substrates for thermogenesis. Carbohydrate metabolism is also affected by THs. Gluconeogenesis and glycogenolysis are known to be enhanced by THs in a process that supports tissues with fuel to maintain their energy requirements. In this sense, hepatic insulin resistance has been shown to increase gluconeogenesis and subsequently hepatic glucose output in hyperthyroid individuals.[13] Increased rates of gluconeogenesis are supported by increased Cori cycle activity, which involves muscle tissue in providing substrates (lactate and certain amino acids such as alanine and glutamine) for hepatic gluconeogenesis. This process represents a dynamic glucose buffer that allows it to be used by other tissues under their glucose requirements as needed. It is known that THs in the liver increase the expression of phosphoenolpyruvate carboxykinase, which is the rate-limiting step in gluconeogenesis, and supports the direct role of THs in the regulation of these processes. Studies in mice exposed to T4 mimicking hyperthyroidism have shown that insulin signaling is active in insulin-target tissues even under fasting conditions due to dysregulated function of the endocrine pancreas (for example, increased insulin secretion followed by circulating levels). Overall, compelling data in the literature suggest that THs produce effects in a few, if not all, tissues involved in glucose and lipid homeostasis.[14]

Changes in Thyroid Hormones in Diabetes Mellitus

The relationship between changes in thyroid function and the development of different types of DM has been the focus of intense research. The prevalence of hyperthyroidism in DM individuals is higher than in nondiabetic subjects, and a study has determined that patients suffering from hyperthyroidism are at higher risk of developing DM. Among adult patients with T2D, ~4.4% have overt hyperthyroidism and 2%-4% have subclinical

hyperthyroidism. Interestingly, improved diabetic control in T2D patients normalizes TSH levels in patients with subclinical hyperthyroidism; this suggests that treatments that improve T2D may contribute to normalizing thyroid function. However, a recent study has shown that nondiabetic patients diagnosed with hyperthyroidism have an increased risk of developing T2D later in life, suggesting that thyroid dysfunction may precede diabetogenic processes.[15] Accordingly, hyperthyroid patients showed increased basal hepatic glucose production and increased fasting insulin levels compared to healthy individuals, while hyperthyroid patients treated with methimazole became euthyroid, exhibiting significantly reduced levels in the same parameters, reaching the levels of the healthy control group. One study showed that patients with overt or subclinical hyperthyroidism undergoing a glucose tolerance test had higher circulating glucose and insulin levels. Glucose intolerance in these patients is due to enhanced hepatic gluconeogenesis.[16] These effects may be related to the control-exerting THs in the expression of genes involved in glucose and lipid metabolism, suggesting that several physiological abnormalities that contribute to the loss of metabolic homeostasis are common in hyperthyroidism and T2D. Another study showed that hypothyroidism is associated with insulin resistance and dyslipidemia. Other evidence also points to an increased risk of DM in patients with hypothyroidism and has reported an increased prevalence of subclinical hypothyroidism in patients with T2D. Other studies have failed to link hypothyroidism with the development of T2D, in contrast to compelling research showing the relationship between DM and thyroid dysfunction, supported by the well-defined role of THs on glucose metabolism and insulin secretion. Increasing evidence links changes in thyroid function with other types of DM, such as T1D and gestational DM (GDM). Various studies have shown that patients with T1DM, an autoimmune disease, are prone to exhibit AITD such as HT and GD. Available data show that up to 30% of adults with T1D have thyroid diseases of autoimmune origin.[17]

Gestational DM is a common complication affecting ~10% of all pregnancies associated with adverse pregnancy outcomes such as preeclampsia, macrosomia, and cesarean delivery. Gestational DM disappears after birth, but in many cases different types of DM (GDM in a subsequent pregnancy or T2DM) can occur later in life. [18] Among the changes that occur during pregnancy, the placenta is known to increase the secretion of pro-inflammatory cytokines that induce insulin resistance to support nutrient availability for the fetus.[46] Under these conditions (e.g., transient insulin resistance during pregnancy), GDM is the result of the impaired capacity of pancreatic β-cells to increase insulin secretion to compensate for insulin resistance in insulin-target tissues. [19] Several reports have identified that maternal hypothyroidism predisposes the offspring to exhibit limited insulin secretion and develop glucose intolerance, increasing the risk of T2D in the offspring.[20] In addition, separate reports have identified hypothyroidism as being associated with GDM. In this regard, we found several mutations in PAX8. It leads to hypothyroidism associated with the development of GDM, suggesting that human GDM may have a genetic component. Remarkably, this study revealed that PAX8 expression in pancreatic islets modulates cellular pathways involved in cellular survival.[21]

The Physiological and Pathophysiological Role of Thyroid Hormones in the Endocrine Pancreas

One of the main organs involved in the control of circulating glucose levels is the endocrine pancreas. Extensive research has demonstrated the role of THs in the differentiation, maturation, and functionality of metabolic tissues.[22] In vivo research has determined that circulating T3 levels increase during postnatal development and induce the expression of MAF bZIP transcription factor A and THRs in pancreatic β-cells to facilitate their maturation.[23] A study on experimental animals showed that TH supplementation had severe effects on β-cells as well as increased β-cell proliferation and apoptosis. Strikingly, β-cells of T4-treated mice have been reported to exhibit increased glucokinase expression. At the organism level, T4-treated mice exhibit increased insulin expression and secretion in pancreatic islets under fasting conditions. This indicates that the insulin secretory mechanism is constitutively active to facilitate nutrient uptake by insulin-target tissues.[14]

Separate investigation in mildly hypothyroid PAX8 heterozygous knockout mice, which exhibit several hallmarks of T2D, demonstrated that pancreatic islets exhibited a transcriptional profile associated with increased metabolic activity and impaired antioxidant capacity.[24] Pancreatic β-cells are particularly vulnerable to oxidative stress due to very limited expression of antioxidant genes such as catalase and glutathione peroxidase (e.g., <5% of hepatic levels). More importantly, under typical cellular stress situations such as high glucose, high oxygen, or heat shock, pancreatic islets have virtually no capacity to increase the expression of antioxidant enzymes. Increased metabolic activity states with limited antioxidant defenses can generate oxidative stress, which can lead to accumulation of oxidative damage. In these cases, pancreatic endocrine function may be compromised and apoptotic processes may be initiated if cellular stress is not resolved.[25]

Thyroid Hormone-Related Changes in Insulin-Target Tissues

Changes in TH function have tremendous effects on liver tissue. Thyroid hormones cause increases in intracellular glucose production and insulin resistance.[26] Thyroid hormone-mediated insulin resistance can be produced by increased levels of cytokines produced in peripheral tissues such as adipose tissue[27] Given the central role of insulin action in the regulation of hepatic gluconeogenesis and glycogenolysis, the compromised insulin sensitivity produced by THs may have important implications of its own for glucose homeostasis.[28] Interestingly, effects on endogenous glucose production in the liver have been shown, in part, to mediate the effects of THs in the paraventricular nucleus of the hypothalamus, which mediates effects via sympathetic projections to the liver.[26] In this regard, Klieverik et al showed that increases in endogenous glucose production mediated by the paraventricular nucleus are independent of circulating levels of glucoregulatory hormone.[29] Furthermore, these studies showed that hepatic sympathetic denervation completely blunted the paraventricular TH-induced increase in endogenous glucose production. Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome. Various changes have been found in the pathogenesis of NAFLD in hypothyroid patients, including the development of insulin resistance, dyslipidemia, and increased adiposity.[30] Epidemiological studies have identified the existence of an inverse correlation between circulating TH levels and the incidence of NAFLD.[31] A study also showed that patients with NAFLD exhibit higher serum TSH levels and lower free T4 levels.[32] Accordingly, hypothyroidism is more common in patients with NAFLD when compared to healthy individuals matched for ethnicity, age, sex, and body mass index. Patients with nonalcoholic steatohepatitis (NASH), a more serious form of fatty liver disease, had a higher incidence of hypothyroidism compared to patients

suffering from NAFLD without NASH. Individuals diagnosed with hypothyroidism were 2.1 times more likely to experience NAFLD and NASH, respectively.[33] In addition, NASH and advanced fibrosis are more common in patients with overt and subclinical hypothyroidism.[34] Interestingly, overt and subclinical hypothyroidism, as well as even upper TSH levels in the euthyroid range, have been associated with NAFLD regardless of established metabolic risk factors.[35] In addition, hypothyroid patients exhibit increased esterification of hepatic fatty acids with restricted lipoprotein lipase activity and decreased hepatic uptake of high-density lipoprotein, indicating an inappropriate cholesterol metabolism.[36]

Thyroid hormones also play an important role in other insulin-targeted tissues such as adipose tissue and skeletal muscle. The association between hypothyroidism and impaired insulin-stimulated glucose uptake in muscle and adipose tissue has been documented in animals and humans.[33,37] However, conflicting results were obtained when hyperthyroid patients were analyzed for positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (18 F-A fluorodeoxyglucose [FDG] -positron emission tomography [PET]/CT). One report showed that hyperthyroid patients exhibit increased uptake of radioactive glucose in brown adipose tissue compared to euthyroid patients.[38] A second study achieved similar results (e.g., increased radioactive glucose uptake) in hypothyroid patients with thyroid carcinoma when these patients became mildly hyperthyroid upon TSH suppression. However, other studies have shown no difference in glucose uptake in patients with hyperthyroidism and in hypothyroid patients with thyrotoxicized thyroid cancer.[39]

Thyroid hormones exert significant effects on energy metabolism, which predisposes tissues and organs with high metabolic demand, such as skeletal muscle, to severe effects in patients suffering from hypothyroidism and hyperthyroidism. In skeletal muscle, glucose uptake represents the limiting step in glucose metabolism and is mediated by plasma membrane glucose transporter 4 (Glut4). Thyroid hormones induce Glut4 expression through a positive TRE (DR+4) region in its promoter, which represents a direct link with carbohydrate metabolism. Studies focusing on determining the physiological and pathophysiological role of THs in skeletal muscle have shown that up to 57% of patients with hypothyroidism show muscle damage manifested by elevated creatine kinase levels.[40]

Remarkably, TH treatment in hypothyroid patients reduced creatine kinase levels and improved muscle complications. Individuals with hyperthyroidism also show muscle weakness, and normalization of TH function in these patients increases muscle strength and muscle cross-sectional area and improves insulin response upon administration of TH in patients and experimental models of hypothyroidism.[24] At the tissue level, THs increase insulin sensitivity in skeletal muscle; this effect is due to the proper conversion of T4 to T3 by DIO2. Accordingly, cell cultures of myotubes developed from DIO2 knockout mice and DIO2 knockout mice exhibit insulin resistance.[41] In vivo research mice treated with T4-treated hyperthyroid have shown that insulin signaling is chronically activated in skeletal muscle lysates, which may be detrimental in the long run.[24]

Treatment Approaches Based on Thyroid Hormones or Thyromimetics for Diabetes Mellitus

As mentioned earlier, hypothyroidism is associated with metabolic disorders that increase the tendency to develop T2DM. Thyroid hormone supplementation reduces the risk of developing this disease by normalizing DM-related parameters such as lipid and lipoprotein levels. Studies in mice have also supported the potential of THs to improve metabolic health. Thyroid hormone supplementation has been shown to increase glucose tolerance in wild-type mice and reduce hyperglycemia[42] in leptin receptor-deficient mice. Remarkably, research in mice has also identified the potential of THs to improve metabolic health and survival in experimental models of T1DM.[43] Our results showed that levothyroxine supplementation blunted the onset of experimental T1DM using the RIP-B7.1 model, which summarizes the β-cell-specific autoimmune attack in patients with T1D.[24] Interventional studies in humans using levothyroxine and the thyroxine enantiomer dextrothyroxine have shown increased serum levels of LDL cholesterol after treatment. However, treatments were discontinued as participants developed serious adverse events, confirming the narrow therapeutic window of interventions based on the use of THs.[44] However, the beneficial effects of interventions based on the use of THs in certain metabolic parameters have prompted the development of thyromimetics as promising agents to improve metabolic health. Newly produced thyromimetics could in principle provide therapeutic benefits in certain cell types or organs, resulting in improved metabolic homeostasis while avoiding side effects.[45] Therefore, fatty liver can be treated with thyromimetics designed to specifically target hepatic tissue. One study determined that the liver can be directly targeted using a glucagon-T3 mixed agonist that mediates selective delivery of T3 to the liver.[24,39] Studies have shown beneficial effects on hepatic steatosis, cholesterol, and triglyceride levels in rodents.[46] However, in some cases, thyromimetics (e.g., eprotirome and 3,5-d iiodothyropropionic acid [DIPTA]) have failed due to ineffectiveness or toxicity in human or preclinical studies.[47] Selective THRβ agonists MGL-3196 and VK2809 have recently been investigated in phase 2 clinical trials as lipid-lowering agents and for the treatment of NASH. The most recent results using MGL-3196 in humans indicate a significant reduction in hepatosteatosis after 12 and 36 weeks of treatment.[48] In addition, VK2809 has been shown to reduce hepatic lipid content and circulating LDL levels. However, given the potential side effects of thyromimetics, a better understanding of their selective metabolic effects and experimental and clinical studies evaluating the long-term effects of these interventions are needed.

CONCLUSION

Thyroid hormones are essential hormones that govern all body metabolism, acting on every cell of the body. Changes in THs leading to different forms of hyperthyroidism and hypothyroidism have been associated with various diseases such as DM. This suggests that TH changes share specific pathogenesis mechanisms in which THs contribute at different stages of DM pathogenesis. Therefore, treatments or interventions designed to treat DM may also have beneficial consequences on DM. Further research is needed to increase knowledge about the changes that occur in the early stages of DM and in diseases associated with THs; this currently limits potential biomarkers and targets to facilitate diagnosis, prognosis, and development of new treatments for DM. The pleiotropic effects of TH changes in different tissues indicate that personalized and precision medicine must be applied to provide the most appropriate treatment for each patient. The narrow therapeutic window of interventions based on the use of natural THs has led to the development of thyromimetics. However, most of the thyromimetics tested to date have failed due to ineffectiveness or toxicity.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Z.K., A.D.K.; Design – Z.K., A.D.K.; Supervision – Z.K., A.D.K.; Literature Search – Z.K., A.D.K.; Writing Manuscript – Z.K.; Critical Review – Z.K., A.D.K.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. *Int J Physiol Pathophysiol Pharmacol*. 2019;11(3):45-63.
2. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol*. 2020;16(7):377-390. [CrossRef]
3. Forouhi NG, Wareham NJ. Epidemiology of diabetes. *Medicine (Abingdon)*. 2014;42(12):698-702. [CrossRef]
4. Redondo MJ, Hagopian WA, Oram R, et al. The clinical consequences of heterogeneity within and between different diabetes types. *Diabetologia*. 2020;63(10):2040-2048. [CrossRef]
5. Ozougwu O. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *J Physiol Pathophysiol*. 2013;4(4):46-57. [CrossRef]
6. Liu YC, Yeh CT, Lin KH. Molecular functions of thyroid hormone signaling in regulation of cancer progression and anti-apoptosis. *Int J Mol Sci*. 2019;20(20):4986.[CrossRef]
7. Gereben B, Zavacki AM, Ribich S, et al. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocr Rev*. 2008;29(7):898-938. [CrossRef]
8. Thvilum M, Brandt F, Brix TH, Hegedüs L. A review of the evidence for and against increased mortality in hypothyroidism. *Nat Rev Endocrinol*. 2012;8(7):417-424. [CrossRef]
9. Pistollato F, Masias M, Agudo P, Giampieri F, Battino M. Effects of phytochemicals on thyroid function and their possible role in thyroid disease. *Ann N Y Acad Sci*. 2019;1443(1):3-19. [CrossRef]
10. Ragusa F, Fallahi P, Elia G, et al. Hashimotos' thyroiditis: epidemiology, pathogenesis, clinic and therapy. *Best Pract Res Clin Endocrinol Metab*. 2019;33(6):101367. [CrossRef]
11. MacFarland SP, Bauer AJ, Adzick NS, et al. Disease burden and outcome in children and young adults with concurrent graves disease and differentiated thyroid carcinoma. *J Clin Endocrinol Metab*. 2018;103(8):2918-2925. [CrossRef]
12. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev*. 2014;94(2):355-382. [CrossRef]
13. Klieverik LP, Janssen SF, van Riel A, et al. Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. *Proc Natl Acad Sci U S A*. 2009;106(14):5966-5971. [CrossRef]
14. López-Noriega L, Cobo-Vuilleumier N, Narbona-Pérez ÁJ, et al. Levothyroxine enhances glucose clearance and blunts the onset of experimental type 1 diabetes mellitus in mice. *Br J Pharmacol*. 2017;174(21):3795-3810. [CrossRef]
15. Celani MF, Bonati ME, Stucci N. Prevalence of abnormal thyrotropin concentrations measured by a sensitive assay in patients with type 2 diabetes mellitus. *Diabetes Res*. 1994;27(1):15-25.
16. Maratou E, Hadjidakis DJ, Kollias A, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. *Eur J Endocrinol*. 2009;160(5):785-790. [CrossRef]
17. Shun CB, Donaghue KC, Phelan H, Twigg SM, Craig ME. Thyroid autoimmunity in Type 1 diabetes: systematic review and meta-analysis. *Diabet Med*. 2014;31(2):126-135. [CrossRef]
18. Seely EW, Solomon CG. Insulin resistance and its potential role in pregnancy-induced hypertension. *J Clin Endocrinol Metab*. 2003;88(6):2393-2398. [CrossRef]
19. Kühl C. Insulin secretion and insulin resistance in pregnancy and GDM. Implications for diagnosis and management. *Diabetes*. 1991;40(suppl 2):18-24. [CrossRef]
20. Karbalaei N, Ghasemi A, Faraji F, Zahediasl S. Comparison of the effect of maternal hypothyroidism on carbohydrate metabolism in young and aged male offspring in rats. *Scand J Clin Lab Investig*. 2013;73(1):87-94. [CrossRef]
21. Martin-Montalvo A, López-Noriega L, Jiménez-Moreno C, et al. Transient PAX8 expression in islets during pregnancy correlates with β-cell survival, revealing a novel candidate gene in gestational diabetes mellitus. *Diabetes*. 2019;68(1):109-118. [CrossRef]
22. Mastracci TL, Evans-Molina C. Pancreatic and islet development and function: the role of thyroid hormone. *J Endocrinol Diabetes Obes*. 2014;2(3):1044.
23. Aguayo-Mazzucato C, Zavacki AM, Marinelarena A, et al. Thyroid hormone promotes postnatal rat pancreatic β-cell development and glucose-responsive insulin secretion through MAFA. *Diabetes*. 2013;62(5):1569-1580. [CrossRef]
24. López-Noriega L, Capilla-González V, Cobo-Vuilleumier N, et al. Inadequate control of thyroid hormones sensitizes to hepatocarcinogenesis and unhealthy aging. *Aging (Albany NY)*. 2019;11(18):7746-7779. [CrossRef]
25. Supale S, Li N, Brun T, Maechler P. Mitochondrial dysfunction in pancreatic β cells. *Trends Endocrinol Metab*. 2012;23(9):477-487. [CrossRef]
26. Klieverik LP, Sauerwein HP, Ackermans MT, Boelen A, Kalsbeek A, Fliers E. Effects of thyrotoxicosis and selective hepatic autonomic denervation on hepatic glucose metabolism in rats. *Am J Physiol Endocrinol Metab*. 2008;294(3):E513-E520. [CrossRef]
27. Gierach M, Gierach J, Junik R. Insulin resistance and thyroid disorders. *Endokrynol Pol*. 2014;65(1):70-76. [CrossRef]
28. Hatting M, Tavares CDJ, Sharabi K, Rines AK, Puigserver P. Insulin regulation of gluconeogenesis. *Ann N Y Acad Sci*. 2018;1411(1):21-35. [CrossRef]
29. Martin U, Davies C, Hayavi S, Hartland A, Dunne F. Is normal pregnancy atherogenic? *Clin Sci (Lond)*. 1999;96(4):421-425. [CrossRef]
30. Waring AC, Arnold AM, Newman AB, Bùzková P, Hirsch C, Cappola AR. Longitudinal changes in thyroid function in the oldest old and survival: the cardiovascular health study all-stars study. *J Clin Endocrinol Metab*. 2012;97(11):3944-3950. [CrossRef]
31. Ludwig U, Holzner D, Denzer C, et al. Subclinical and clinical hypothyroidism and non-alcoholic fatty liver disease: a cross-sectional study of a random population sample aged 18 to 65 years. *BMC Endocr Disord*. 2015;15:41. [CrossRef]
32. Xu C, Xu L, Yu C, Miao M, Li Y. Association between thyroid function and nonalcoholic fatty liver disease in euthyroid elderly Chinese. *Clin Endocrinol (Oxf)*. 2011;75(2):240-246. [CrossRef]
33. Pagadala MR, Zein CO, Dasarathy S, Yerian LM, Lopez R, McCullough AJ. Prevalence of hypothyroidism in nonalcoholic fatty liver disease. *Dig Dis Sci*. 2012;57(2):528-534. [CrossRef]
34. Kim D, Kim W, Joo SK, Bae JM, Kim JH, Ahmed A. Subclinical hypothyroidism and low-normal thyroid function are associated with nonalcoholic steatohepatitis and fibrosis. *Clin Gastroenterol Hepatol*. 2018;16(1):123-131.e1. [CrossRef]
35. Bano A, Chaker L, Plompen EP, et al. Thyroid function and the risk of nonalcoholic fatty liver disease: the Rotterdam study. *J Clin Endocrinol Metab*. 2016;101(8):3204-3211. [CrossRef]
36. Pearce EN. Hypothyroidism and dyslipidemia: modern concepts and approaches. *Curr Cardiol Rep*. 2004;6(6):451-456. [CrossRef]
37. Rochon C, Tauveron I, Dejax C, et al. Response of glucose disposal to hyperinsulinaemia in human hypothyroidism and hyperthyroidism. *Clin Sci (Lond)*. 2003;104(1):7-15. [CrossRef]
38. Lahesmaa M, Orava J, Schalin-Jäntti C, et al. Hyperthyroidism increases brown fat metabolism in humans. *J Clin Endocrinol Metab*. 2014;99(1):E28-E35. [CrossRef]
39. Gavrila A, Hasselgren PO, Glasgow A, et al. Variable cold-induced brown adipose tissue response to thyroid hormone status. *Thyroid*. 2017;27(1):1-10. [CrossRef]

40. Torrance CJ, Usala SJ, Pessin JE, Dohm GL. Characterization of a low affinity thyroid hormone receptor binding site within the rat GLUT4 gene promoter. *Endocrinology*. 1997;138(3):1215-1223. [CrossRef]
41. Marsili A, Aguayo-Mazzucato C, Chen T, et al. Mice with a targeted deletion of the type 2 deiodinase are insulin resistant and susceptible to diet induced obesity. *PLoS One*. 2011;6(6):e20832. [CrossRef]
42. Lin Y, Sun Z. Thyroid hormone potentiates insulin signaling and attenuates hyperglycemia and insulin resistance in a mouse model of type 2 diabetes. *Br J Pharmacol*. 2011;162(3):597-610. [CrossRef]
43. Verga Falzacappa C, Patriarca V, Bucci B, et al. The TRbeta1 is essential in mediating T3 action on Akt pathway in human pancreatic insulinoma cells. *J Cell Biochem*. 2009;106(5):835-848. [CrossRef]
44. Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med*. 2008;148(11):832-845. [CrossRef]
45. Finan B, Clemmensen C, Zhu Z, et al. Chemical hybridization of glucagon and thyroid hormone optimizes therapeutic impact for metabolic disease. *Cell*. 2016;167(3):843-857.e14. [CrossRef]
46. Cable EE, Finn PD, Stebbins JW, et al. Reduction of hepatic steatosis in rats and mice after treatment with a liver-targeted thyroid hormone receptor agonist. *Hepatology*. 2009;49(2):407-417. [CrossRef]
47. Ladenson PW, McCarren M, Morkin E, et al. Effects of the thyromimetic agent diiodothyropropionic acid on body weight, body mass index, and serum lipoproteins: a pilot prospective, randomized, controlled study. *J Clin Endocrinol Metab*. 2010;95(3):1349-1354. [CrossRef]
48. Sinha RA, Bruinstroop E, Singh BK, Yen PM. Nonalcoholic fatty liver disease and hypercholesterolemia: roles of thyroid hormones, metabolites, and agonists. *Thyroid*. 2019;29(9):1173-1191. [CrossRef]