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ORIGINAL ARTICLE

Diabetes: Insights into Thyroid Hormones

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ABSTRACT

Numerous physiological and pathological processes must be controlled for the thyroid gland to function properly. Research utilising both animal models and human subjects has demonstrated that thyroid hormones regulate cellular processes that are crucial for most age-related diseases. Furthermore, both hyperthyroidism and hypothyroidism have been associated to the onset of several kinds of diabetes, proving the intricacy of the molecular processes regulated by thyroid hormones. In this article, we provide a summary of the most recent thyroid hormone-related findings in the field of diabetes research. We contend that despite the difficulty in developing thyromimetics due to their inefficiency and potential toxicity, therapies based on the use of modulators of thyroid hormone activity may be therapeutically beneficial in some kinds of diabetes.

INTRODUCTION

The production of thyroid hormone (TH) is carefully regulated by a negative feedback loop that involves the hypothalamus, the pituitary gland, and the thyroid axis (Figure 1). The hypothalamus is responsible for the production of TRH. After being secreted, TRH causes an increase in the synthesis of TSH by interacting with a receptor for TRH in the pituitary gland (Liu et al., 2019). Within the thyroid, TSH binds to TSHR to stimulate the production of TH by the thyroid. The hormones triiodothyronine (T3) and tetraiodothyronine (T4) are only secreted when they are required. THs are responsible for maintaining constant levels of TRH, TSH, and TH by completing a negative feedback loop that restricts the production and secretion of TRH and TSH via THR in the hypothalamus and pituitary gland.

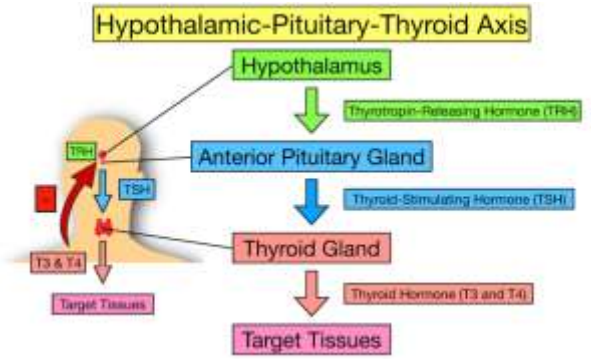

Figure 1: Thyroid Hormone Production and Function Scheme

Deiodinases (DIO2 and DIO3) take T4 as their starting material and remove the 5′ iodine to create T3. Regardless of the amounts of circulating TH, the effects of TH are controlled by the production of deiodinase that is cell-type and tissue-specific (Schweizer et al., 2008). Binding of intracellular T3 occurs via the TH receptor (THR) and the THR, both of which have a high affinity for the TH response components (TREs). THRs are known to form a transcription co-activator complex when they bind to their respective ligands (Perissi et al., 2010). THR is known to have interactions with a variety of different nuclear hormone receptors, including peroxisome proliferator-activated receptors, retinoid X receptors, retinoic acid receptors, and liver X receptors. Because of this, binding to a wide variety of nucleotide sequences that regulate different metabolic pathways, such as cholesterol, glucose, and fatty acid metabolism, is made possible (Kouidhi and Clerget-Froidevaux, 2018). PI3 K-AKT-FOXO1 and mTOR-p70S6 K signalling are two examples of protein-protein interactions that are examples of additional ways that THs influence transcription (Flamant et al., 2017). THRs influence more than 80 genes, the majority of which are involved in processes such as de novo lipogenesis, the tricarboxylic acid cycle, oxidative phosphorylation, mitochondrial biogenesis, and the catabolism of fatty acids (Singh et al., 2018). Catabolism of all forms of energy can be attributed to THs due to their ability to increase oxygen consumption, ATP hydrolysis, and mitochondrial coupling (Johannsen et al., 2012). THs have the effect of elevating the basal metabolic rate, often known as the energy expenditure at rest. THs are essential to both the growth of tissues and the maintenance of overall health (Ng et al., 2013). TSH levels can range anywhere from 0.39 to 4.6 mIU/L, whereas total T4 levels can be anywhere from 57.9 to 169.9 nM. (Hollowell et al., 2002). TH changes should fall somewhere in the range of 0.5 percent to 4 percent in regions that receive an acceptable amount of iodine.

Clinical hypothyroidism, also known as overt hypothyroidism (Taylor et al., 2013), is linked to metabolic dysregulations that heighten the risk of cardiovascular issues and diabetes mellitus (DM), including hypercholesterolemia and elevated LDL levels. Subclinical hypothyroidism has been linked to poor neurocognitive health, an unbalanced bone metabolism, type 2 diabetes (T2DM), cardiovascular risk factors including high LDL and VLDL levels, hypertriglyceridemia, hypertension, atrial fibrillation, and obesity, as well as low HDL levels and early mortality (Biondi et al., 2019). Patients who have hyperthyroidism have an increased risk of developing diabetes and cardiovascular issues, both of which can lead to mortality at an earlier age (Brandt et al., 2013). Subclinical hyperthyroidism with low TSH levels is associated with an increased risk of neurocognitive impairment and dementia (Aubert et al., 2017). The risk of fracture is elevated in patients with both overt and subclinical hyperthyroidism (Blum et al., 2015).

Thyroid hormones in diabetes mellitus

Thyroid hormones and glucose/lipid metabolism: The breakdown of accumulated energy occurs because of THs increasing the body's need for oxygen (Johannsen et al., 2012). THs regulate the metabolism of lipids and glucose. THs reduce triglycerides and lipoproteins with high levels of cholesterol. THs boost the expression of Srebp2 (Mullur et al., 2014). Srebp-2 increases the expression of LDL receptors, which causes an increase in hepatic cholesterol uptake. In the body, THs promote both lipolysis and lipogenesis. Both acetyl-coenzyme A carboxylase and carnitine palmitoyl transferase I, which are involved in lipogenesis and mitochondrial fatty acid absorption, are increased by THs (Mullur et al., 2014). An in-depth analysis of these processes reveals that in the context of considerable lipolysis, liponeogenesis must be increased to maintain stable lipid levels (Oppenheimer et al., 1991). In these conditions, lipolysis acts to promote thermogenesis. TH may have an impact on how carbs are metabolised.

THs activate gluconeogenesis and glycogenolysis to produce the energy that the tissues need. The impact of hyperthyroidism on insulin resistance in the liver leads to increased gluconeogenesis and glucose production in the liver (Figure 2) (Potenza et al., 2009). Hepatic gluconeogenesis, which increases in direct proportion to the amount of activity in the Cory cycle, uses substrates from muscle tissue as a source (lactate and certain amino acids such as alanine and glutamine). As a result, a glucose buffer is created, which other tissues can utilise as needed. The fact that THs increase the expression of the rate-limiting step in the process of gluconeogenesis, phosphoenolpyruvate carboxykinase, implies that they directly regulate these activities. Studies in mice exposed to T4 imitating hyperthyroidism shown that insulin signalling remains active in insulin-target organs even under fasting conditions because of a disturbed endocrine pancreas. For instance, elevated circulation levels and insulin secretion (Lopez-Noriega et al., 2017). Overall, studies have revealed that THs have an impact on most, if not all, of the tissues that control glucose and lipids (Figure 2).

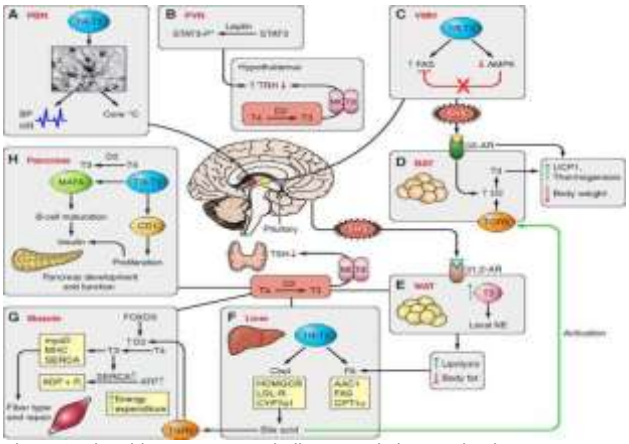

Figure 2: Thyroid Hormone Metabolism Regulation Mechanism

Thyroid hormones in diabetes: Many studies have investigated the possible connection between thyroid function and diabetes. According to Biondi et al. (2019), people who have diabetes are more likely to have hyperthyroidism than people who do not have diabetes. Furthermore, a study conducted in Denmark indicated that people who already have hyperthyroidism had a greater risk of developing diabetes (Brandt et al., 2013). Patients with type 2 diabetes who have overt hyperthyroidism make up 4.4% of the population, while between 2% and 4% have subclinical hyperthyroidism (Biondi et al., 2019). TSH levels in patients with subclinical hyperthyroidism are brought back to normal when diabetes control is improved in T2DM patients, which suggests that T2DM treatments may be able to normalise thyroid function (Celani et al., 1994). Recent studies demonstrate that thyroid dysfunction may precede diabetogenic processes in non-diabetic people with hyperthyroidism (Chen et al., 2019). Patients suffering from hyperthyroidism have higher basal hepatic glucose production as well as increased fasting insulin levels in comparison to healthy persons. Patients diagnosed with hyperthyroidism who were treated with methimazole and subsequently declared euthyroid had considerably reduced levels on the same metrics, reaching the amounts of the strong control group (Cavallo-Perin et al., 1988). Patients with explicit or subclinical hyperthyroidism who underwent a glucose lenience test had developed glucose and insulin levels, according to the findings of an experiment that was conducted independently. In these patients, intolerance to glucose is brought on by an increase in hepatic gluconeogenesis (Maratou et al., 2010). These possessions may be associated to the mechanism that THs have over the expression of genetic factor that are concerned in the metabolism of glucose and lipids, which recommends that hyperthyroidism and type 2 diabetes have similar physiological abnormalities that lead to metabolic dysregulation.

Studies that followed participants over time looked at the connection between thyroid function and diabetes and metabolic syndrome in elder people (Heima et al., 2013; Waring et al., 2012). At the beginning of the study, patients with metabolic syndrome had higher TSH levels than other people. Higher TSH levels were connected to metabolic syndrome even in persons whose levels fell below the normal array (Waring et al., 2012). Another Dutch longitudinal study connected metabolic syndrome and obesity to higher TSH. This investigation was conducted in Amsterdam (Heima et al., 2013). There is a correlation between hypothyroidism, insulin resistance, and dyslipidaemia (Gierach and Junik, 2015; Wang, 2013; Dimitriadis et al., 2006). Hypothyroidism is associated with an increased risk of diabetes, and a comprehensive investigation indicated that subclinical hypothyroidism is prevalent in people with type 2 diabetes (Gronich et al., 2015). Other studies have not been able to establish a link between hypothyroidism and the onset of type 2 diabetes (Ishay et al., 2009; Radaideh et al., 2004).

Modifications in thyroid dysfunction have been linked to the development of gestational diabetes as well as type 1 diabetes (T1DM). People who have type 1 diabetes, an autoimmune disorder, have been shown to have a significantly higher chance of acquiring Hashimoto's thyroiditis and Graves' disease, according to the findings of a number of studies. Diabetes type 1 is an autoimmune disorder. Thirty percent of those who were diagnosed with type 1 diabetes also had issues with their autoimmune thyroid (Shun et al., 2014). The human leukocyte antigen, the cytotoxic T-lymphocyte-associated antigen 4, protein tyrosine phosphatase non-receptor type 22, forkhead box P3, and the interleukin-2 receptor alpha/CD25 gene region are all examples of susceptibility genes (Dittmar and Kahaly, 2010). These genetic materials influence the immunologic synapse as well as the activation of T cells, which suggests that T1D and autoimmune thyroid illnesses share comparable pathogenic pathways (Dittmar and Kahaly, 2010).

Diabetes mellitus during pregnancy affects around 10% of pregnancies and has been associated to macrosomia, preeclampsia, and caesarean delivery (IAD, 2010; Petra et al., 2019). GDM usually vanishes after birth, however it can come back at a later age. During pregnancy, the placenta produces pro-inflammatory cytokines to increase the amount of food that is readily available to the developing foetus (Kim et al., 2010). The failure of pancreatic cells to boost insulin secretion in order to compensate for fleeting insulin resistance is the primary contributory factor in the development of type 2 diabetes (such as that which occurs during pregnancy). Because of lower insulin production and higher glucose intolerance, hypothyroidism in mothers has been associated to an increased risk of type 2 diabetes in their offspring. This is because hypothyroidism in mothers' results in decreased insulin production. Multiple studies have found a connection between hypothyroidism and GDM (Martin-Montalvo et al., 2019). There is a connection between GDM and numerous transformations in PAX8 that can lead to hypothyroidism, which suggests a genetic module (Martin-Montalvo et al., 2019). Expression of PAX8 in pancreatic islets influences many survival pathways (Martin-Montalvo et al., 2019).

The involvement of thyroid hormones in the endocrine pancreas: Endocrine pancreas modulates blood glucose levels. Extensive study has demonstrated that THs are important for the formation, maturity, and function of metabolic tissue (Figure 2) (Mastracci and Evans-Molina, 2014). During postnatal development, there is an increase in the amount of T3 in the blood, which stimulates the creation of MAFA and THRs in pancreatic compartments. This helps the cells mature more quickly (Aguayo-Mazzucato et al., 2011; Aguayo-Mazzucato et al., 2013; Aguayo-Mazzucato et al., 2015). Experiments conducted on mature wild-type mice reveal that treatment with TH leads to an increase in both apoptosis and cell proliferation (Lopez-Noriega et al., 2017).

More glucokinase (GK) is expressed in mouse cells that have been treated with T4 (Figure 2). Increased GK activity might make it possible to achieve a high rate of cell turnover by hastening the processes of cell growth and death (Lopez-Noriega et al., 2017). THs are responsible for the ageing of cells because they induce p16INK4A expression (also known as CDKN2A). When THs bind to THRs, this results in senescence and the maturation of -cells (MAFA) (p16INK4A). Both THR1 and THR bind to TRE site 2 on MAFA, but THR predicaments to TRE position 5 on CDKN2A (Aguayo-Mazzucato et al., 2018). At the organismal level, T4-treated mice express and secrete more insulin in pancreatic isles during abstaining, demonstrating that the insulin discharge mechanism is constitutively functioning to ease nutrition uptake by insulin-target tissues. This is important because fasting causes pancreatic islets to express and secrete more insulin (Figure 2) (Lopez-Noriega et al., 2017).

Pancreatic islets have been demonstrated to demonstrate a transcriptional contour that relates to enhanced metabolic pursuit and lower antioxidant capabilities, according to other studies conducted on mice with moderate hypothyroidism that were PAX8 heterozygous knockouts (Lopez-Noriega et al., 2019). Because catalase and glutathione peroxidase expression are low in pancreatic cells (less than 5 percent of the levels found in the liver), pancreatic cells are sensitive to oxidative stress (Tiedge et al., 1997). Pancreatic islets almost completely lack the capability to improve the utterance of antioxidant enzymes in response to cellular stresses such as increased glucose levels, enchanted oxygen levels, or high temperatures (Tiedge et al., 1997). Oxidative stress and damage can be caused when metabolic activity is increased while antioxidant defences are decreased. Under these conditions, cellular stress may promote pancreatic apoptosis and affect the endocrine function of the pancreas (Supale et al., 2012).

TH-related variations in insulin-target tissues: The liver tissue is significantly affected by changes in TH (Figure 2). THs oversee causing the resistance of insulin and glucose (Klieverik et al., 2008). Possible causes of TH-reconciled insulin resistance include cytokines released by adipose tissues (Mitrou et al., 2010; Gierach et al., 2014). Since insulin regulates hepatic gluconeogenesis and glycogenolysis, TH-induced insulin resistance can significantly affect glucose homeostasis (Hatting et al., 2018).

To some extent, the effects that have on the endogenous glucose production of the liver are mediated by the THs that are located in the paraventricular nucleus of the hypothalamus (Klieverik et al., 2008, 2009). The researchers that made this discovery observed that increases in endogenous glucose production that are mediated by the paraventricular nucleus are not related to circulating glucoregulatory hormones in this particular aspect (Klieverik et al., 2009). Denervation of the hepatic sympathetic nerve has the additional effect of completely blocking the surge in endogenous glucose synthesis that is generated by paraventricular TH. This is an extra impact of hepatic sympathetic denervation.

The liver is where the metabolic syndrome manifests itself as NAFLD. The three causes of NAFLD in hypothyroid people are increased adiposity, dyslipidemia, and insulin resistance (Waring et al., 2012). Epidemiological studies have found a relationship between circulating TH and NAFLD that goes in the other direction (Ludwig et al., 2015). Another body of research found that people with NAFLD have elevated blood TSH amounts and reduced free T4 levels (Xu et al., 2011). Even after adjusting for variables like ethnicity, age, gender, and body mass index, patients with NAFLD exhibited a greater rate of hypothyroidism. Patients with NASH had a higher rate of hypothyroidism than NAFLD patients without NASH. Patients with hypothyroidism have a 2.1 ($p = 0.02$) and 3.8 (p 0.001) times higher likelihood of developing NAFLD or NASH (Pagadala et al., 2012). Patients with hypothyroidism are more likely to develop NASH and severe fibrosis (Kim et al., 2018). Greater TSH amounts in the euthyroid scope have also been linked to non-alcoholic fatty liver disease (NAFLD), regardless of metabolic risk variables, in addition to overt and subclinical hypothyroidism (Bano et al., 2016). An upsurge in the esterification of hepatic fats, a decrease in HDL absorption, and a decrease in lipoprotein lipase activity are all signs of aberrant cholesterol metabolism in people with hypothyroidism. It was discovered that mice with moderate hypothyroidism brought on by PAX8 heterozygous mice had risen hepatic CD36 utterance (Lopez-Noriega et al., 2019). Fatty acid translocase CD36 enhanced CD36-mediated fat absorption may cause lipid accrual of liver in rats with slight hypothyroidism (Pepino et al., 2014).

THs have a key function in skeletal muscle, an insulin-target tissue, in addition to adipose tissue (Figure 2). Hypothyroidism reduces insulin-induced glucose absorption in skeletal muscular tissue and adipose tissue of animals and people (Pagadala et al., 2012; Dimitriadis et al., 2006). In individuals with hyperthyroidism, the 18F-FDG PET/CT scan results were all over the place.

According to the results of one study, hyperthyroid patients absorb radioactive glucose in the BAT at a faster rate than euthyroid people (Lahesmaa et al., 2014). In a subsequent clinical experiment, patients with thyroid carcinomas and hypothyroidism who received TSH suppression developed moderate hyperthyroidism (Broeders et al., 2016). Other studies' findings (Zhang et al., 2014) show that people with thyrotoxic thyroid cancer who are hypothyroid or hyperthyroid do not differ in how much glucose they consume (Gavrila et al., 2017).

T4 treatment over a 14-day period increased radioactive glucose absorption in suprascapular and subcutaneous WAT (Figure 2). The expression of the thermogenic genes UCP1 and DIO2, respectively, has significantly increased, according to research using transcriptional techniques. It's probable that the effects of TH on WAT are more physiologically important given the contradictory results regarding the function of BAT in hyperthyroid individuals. Triiodothyroacetic acid increases the quantity of UCP1 in gut WAT, according to investigations on rats (Medina-Gomez et al., 2008) The THR analogue sobetirome causes subcutaneous fat in obese animals to become brown (Lin et al., 2015). Sobetirome reduced BAT thermogenic activity in ob/ob mice, indicating that the browning of WAT is the mechanism underlying its metabolic benefits. Hypothyroidism accelerates the browning of WAT (Weiner et al., 2016). Weiner and colleagues found that browning indicators, such as decreased BAT activity and multilocular expression of the protein UCP1, are present in different areas of hypothyroid mice's WATs (Weiner et al., 2016). Browning of the WAT occurs because of decreased BAT function.

The regulation of energy metabolism by THs can have detrimental effects on tissues and organs like skeletal muscle, which have a high metabolic demand (Figure 2). Glucose transporter 4, which is found in the plasma membrane, mediates the glucose absorption process in skeletal muscle (Glut4).

Due to a certain TRE (DR+4) site in the promoter of the gene for Glut4, which connects glucose metabolism to THs, this gene's expression is activated (Torrance et al., 1997). Creatine kinase results show that up to 57% of hypothyroidism patients have suffered some sort of muscle injury (Hekimsoy and Oktem, 2005). Because of TH medication, creatine kinase levels were reduced, and musculoskeletal problems were cured (Hekimsoy and Oktem, 2005).

Patients with hyperthyroidism whose TH function is restored have gains in muscular strength and cross-sectional area (Brennan et al., 2006). It has been demonstrated that TH improves insulin sensitivity in hypothyroid people and hypothyroid animal models (Lopez-Noriega et al., 2019). THs increase skeletal muscle insulin sensitivity, which is dependent on DIO2 converting T4 to T3 in the first place. Insulin resistance in myotube cell cultures from DIO2 mutant mice (Marsili et al., 2011). An in vivo experiment using mice with hyperthyroidism revealed that extended insulin signalling in skeletal muscle lysates may be harmful (Figure 2) (Lopez-Noriega et al., 2019)

Diabetes therapy using thyroid hormones or thyromimetics: Hypothyroidism, which causes metabolic instability, significantly

raises the chance of developing type 2 diabetes. Diabetes risk factors such as cholesterol and lipoprotein levels can be brought back to normal with TH supplementation (Tzotzas et al., 2000). Research conducted on mice has demonstrated that thyroid hormones (THs) have the potential to improve metabolic health. The ability of mice to tolerate glucose is improved when it is supplemented with TH, and hyperglycemia is decreased in mice that are deficient in leptin receptors (Lopez-Noriega et al., 2017). It has been shown that administration of THs improves metabolic health and increases the likelihood of survival in animal models of type 1 diabetes (Lopez-Noriega et al., 2017). In the RIP-B7.1 model, which simulates the cell-specific autoimmune response that is seen in people who have Type 1 Diabetes, treatment with levothyroxine prevented the development of Type 1 Diabetes, which is an experimental form of the disease (Lopez-Noriega et al., 2017). In investigations conducted on humans, it was found that both levothyroxine and dextrothyroxine were effective at lowering LDL cholesterol. The fact that the participants had substantial adverse effects demonstrates the limited therapeutic window offered by TH-based therapy (Ochs et al., 2008). Even though TH-based therapies are beneficial for specific metabolic indicators, thyromimetics have been studied as potential medications with the goal of improving metabolic health. Recent advances in the field of thyromimetics have the potential to reduce the severity of adverse effects while simultaneously restoring metabolic homeostasis (Finan et al., 2016). To treat fatty liver disease, thromimetic medications, which specifically target the hepatic tissue, are typically used. According to the findings of Finan et al. (2016) a glucagon-T3 mixed agonist has the capability to transport T3 preferentially to the liver. Given the importance of THs in these organs, it is possible that it will be possible to target the white adipose tissue (WAT), the brown adipose tissue (BAT), or the pancreatic islets (Lopez-Noriega et al., 2017; Gavrila et al., 2017).

Several independent studies have been conducted to investigate the possibility that medications that target THR1 or THR1 could be beneficial to some tissues without having an adverse effect on other tissues (Mishra et al., 2010). Both eprotirome and sobetirome lower levels of circulating LDL cholesterol, however neither one influences heartbeat rate (Martagon et al., 2015). The benefits of reducing hepatic cholesterol, steatosis, and triglyceride levels in animals have been proven in several trials that were conducted separately (Cable et al., 2009). A variety of thyromimetics, such as eprotirome and DIPTA, have been shown to be ineffective in human or preclinical investigations. This is likely because to the high levels of toxicity exhibited by these substances (Sjouke et al., 2014). In the existing phase 2 clinical study, the selective THR agonists MGL3196 and VK2809 are being investigated for their potential use as therapies for NASH and as cholesterol-lowering medicines (Sinha et al., 2019; Lonardo et al., 2017). After 12 and 36 weeks of treatment, it has been established that the use of MGL-3196 is useful in reducing the severity of hepatosteatosis in persons (Sinha et al., 2019; Harrison et al., 2019). The levels of hepatic cholesterol and LDL are lowered with the use of VK2809 (Sinha et al., 2019). Experimentation and clinical study into the long-term effects of thyromimetics are an absolute necessity since it is highly likely that these treatments will have undesirable side effects. The therapeutic potential of thyromimetics has been demonstrated in a significant number of different clinical diseases. Site-specific TH modulators are currently the focus of a sufficient amount of research to warrant further investigation into their viability as potential treatments for diabetes and other illnesses.

CONCLUSION

The THs oversee the metabolism of the entire cell in the body. Alterations in the function of THs have been related to various states of health and illness, ranging from a long life in those with low thyroid activity to death in people who do not have THs. Alterations in thyroid hormone levels that can cause hyperthyroidism or hypothyroidism have been linked to age-related diseases such as diabetes (DM). The fact that fluctuations in TH levels are linked to diabetes pathogenesis demonstrates that THs have a role in the development of diabetes. It is difficult to resist the notion that DM treatments might slow down ageing and increase life expectancy. It is necessary to conduct additional research to raise awareness of early TH changes that are associated with diabetes. Without this awareness, it will be difficult to find new biomarkers and targets that can assist with the diagnosis, prognosis, and the development of innovative DM therapeutics. Because of the pleiotropic effects that TH alterations have in a variety of tissues, each patient's medicine needs to be individualised and precise. Because the therapeutic window for naturally occurring THs is so narrow, thyromimetic drugs were developed. The majority of thyromimetics that have been tested too this far have either been unsuccessful or hazardous. A recent study suggests that thyromimetics that are both safe and effective may provide therapeutic assistance for a variety of diseases, including diabetes.

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