Interplay between Thyroid Disorders and T2DM

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Thyroid disorders (TD) and diabetes mellitus (DM) are the two endocrinopathies with the highest prevalence in the general population that frequently coexist. Thyroid dysfunction is more common in people with type 2 diabetes mellitus (T2DM) compared to normoglycemic individuals. Untreated TD can impair glycemic control, increasing the risk of diabetes complications. Hyperinsulinemia can affect the morphology of the thyroid gland by promoting the proliferation of thyroid tissue and increasing the size of thyroid nodules. Metformin can confer benefits in both endocrinopathies, while other antidiabetics, such as sulfonylureas, can negatively affect thyroid function.

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

1. The Interplay between Thyroid Hormones and Glucose Homeostasis

Thyroid hormones (THs) affect the regulation of glucose homeostasis and lipid metabolism through both the central nervous system and directly in peripheral target organs such as the liver, skeletal muscle, pancreatic beta cells, and white and brown adipose tissues [1]. In particular, THs enhance glucose absorption by the gastrointestinal tract and increase hepatic gluconeogenesis through increased activity of the enzyme phosphoenolpyruvate carboxykinase (PEPCK) [2]. The consequences of increased glycogenolysis and increased hepatic glucose output are hyperinsulinemia and glucose intolerance, leading to insulin resistance [3]. Furthermore, THs increase lipolysis in adipose tissue, leading to a slight elevation in serum-free fatty acid levels within the normal range. Excess THs can even cause insulin resistance [2]. THs increase glucose uptake by skeletal muscle through expression of the GLUT4 gene and increase insulin and glucagon secretion by beta and alpha pancreatic cells, respectively [2].

A large-scale cross-sectional study by Gu et al. [4] demonstrated that TSH, FT4, and FT3 levels correlate with the risk of T2DM, even if they are within the normal reference range. More specifically, after adjustment for various confounders in both men and women, there was a higher prevalence of T2DM among the adult population in individuals with reduced FT3 levels, FT3/FT4 ratio, and increased levels of FT4, and this finding was independent of age. Furthermore, a significant inverse correlation was observed between TSH and the prevalence of T2DM in men, although this observation was not replicated in women.

TSH stimulates deiodinase expression and activity [5][6]. Elevated peripheral deiodinase activity increases the conversion of FT4 to FT3 and the basal metabolic rate, which is important for the regulation of adipose tissue homeostasis [7][8]. Conversely, a suppression of peripheral deiodinase activity lowers the basal metabolic rate. Therefore, the FT3/FT4 ratio can be considered as a marker of peripheral deiodinase activity in T2DM.

Insulin resistance and excess insulin release observed in DM induce the proliferation of the thyroid gland, thus increasing the incidence, size, and volume of thyroid nodules [9][10]. Furthermore, among those with T2DM and thyroid nodules, females have a larger nodule volume and size that are positively associated with the magnitude of insulin resistance [10]. Periodic changes in female endocrine hormones may be related to the higher frequency of thyroid nodules in women [11]. In patients with T2DM, insulin resistance is a risk factor for thyroid nodules. Reducing insulin resistance can slow their growth rate and decrease both their volume and size [10].

DM interferes with thyroid function by modifying TSH levels and inhibiting the conversion of T4 to T3 in peripheral tissues [9][12]. In individuals with DM and normal thyroid function, the nocturnal TSH peak has been found to be absent or weak, and the TSH response to thyrotropin-releasing hormone (TRH) is also impaired [13]. Adipose tissue releases several hormonal mediators, such as leptin, which have been found to be elevated in T2DM patients. Leptin stimulates the hypothalamus–pituitary–thyroid axis, which in turn raises TSH levels [14]. Moreover, acute situations such as diabetic ketoacidosis can confound laboratory tests of thyroid function by decreasing T3 and T4 levels while TSH levels remain unchanged [15]. In individuals with hypothyroidism, the efficacy of TH replacement could be affected by coexisting DM [9].

Visceral adiposity is positively correlated with insulin resistance and the risk of T2DM [16]. TSH levels have been proven to be associated with the degree of obesity in people with normal thyroid function, and TSH levels are higher in people with obesity compared to controls [17]. The main mechanism that leads to the elevation of TSH in this population is the increased secretion of leptin by adipose tissue [18]. A positive correlation has been reported between serum leptin and TSH levels [19][20][21]. Furthermore, it has been shown that there is a significant and positive association between serum TSH, even within the normal range, and BMI. Patients with SCH who lost weight after bariatric surgery improved or normalized their TH levels [22]. Therefore, it is evident that people with DM have higher levels of leptin secretion, which can stimulate TSH synthesis through the hypothalamic–pituitary–thyroid axis [23]. Excess insulin can modulate glycemic levels and, furthermore, may induce an elevation of TRH and TSH [24]. From a clinical perspective, complications such as diabetic nephropathy, diabetic retinopathy, peripheral arterial disease, and diabetic peripheral neuropathy were observed to occur more frequently in individuals with T2DM and SCH [25].

2. Specific Thyroid Disorders and Type 2 Diabetes Mellitus

2.1. Hyperthyroidism

TH excess leads to several alterations in peripheral organ targets and induces hyperglycemia and insulin resistance. THs exert a key role in hepatic glucose metabolism, with stimulative effects on liver glucose production and insulin requirement. They stimulate the hepatic expression of the glucose transporter GLUT2, resulting in increased hepatic glucose output [26]. Also, in hyperthyroid individuals, there is an increase in mRNA expression and activity of the enzyme PEPCK and other hepatic gluconeogenic enzymes, which enhance gluconeogenesis and glycogenolysis, eventually leading to the development of liver insulin resistance [27]. Additionally, epinephrine and glucagon have gluconeogenic and glycogenolytic effects on the liver, which are assisted by THs through the affection of b2-adrenergic receptor mRNA and the suppression of inhibitory G protein RNA of the adenylate cyclase cascade [28]. Furthermore, increased lipogenesis and lipolysis are induced by THs and exaggerate the liver glucose and lipid metabolism imbalance, leading to insulin resistance [26].

Unlike the liver, THs act synergistically with insulin in the peripheral tissues. T3 upregulates the expression of GLUT4, adenosine monophosphate-activated protein kinase, and acetyl coenzyme A carboxylase, which are involved in basal and insulin-stimulated glucose transport, utilization, and glycolysis in skeletal muscle [29][30]. T3 upregulates mitochondrial uncoupling protein (UCP)3, leading to the increased energy expenditure seen in hyperthyroidism [31]. Skeletal muscle and adipose tissue exert opposite effects. Skeletal muscles produce several myokines that affect adipose tissue, while adipose tissue delivers adipokines that can modulate the insulin sensitivity of skeletal muscle. Both hyperthyroidism and hypothyroidism intervene in this pathway, thus contributing to insulin resistance [32]. Insulin-stimulated glucose oxidation rate increases in muscle and adipose tissue of patients with hyperthyroidism. Increased lipolysis is also observed in the adipose tissue of hyperthyroid individuals, leading to elevated free fatty acid levels. A hypermetabolic state is seen in patients with hyperthyroidism, and pre-existing glucose intolerance can be aggravated. Hyperthyroid individuals are at increased risk of severe hyperglycemia, and in the context of insulin deficiency, elevated lipolysis, and hepatic b-oxidation may induce ketoacidosis [2].

In the normal range, T3 influences insulin production by pancreatic beta cells since neonatal beta cells have TH receptors, and their exposure to T3 promotes the activation of the transcription factor MAFA, which stimulates beta cell maturation. However, in hyperthyroid rats, the pancreas is seen to increase, but both the islets' capacity and the overall number of insulin-positive cells are decreased. A significant decline in islet function and decreased glucose-induced insulin production appear to be caused by a decrease in beta cell mass and dysfunction of the insulin secretory pathway, which involves two essential components: ATP-sensitive K^+ and L-type Ca^{2+} channels. Abnormal glucose tolerance is not caused by insulin resistance but rather by a defective pancreatic beta cell response to glucose [33][34][35]. Furthermore, increased insulin degradation and accelerated insulin clearance are observed in individuals with hyperthyroidism [36].

2.2. Hypothyroidism

Patients with hypothyroidism may also develop insulin resistance, although there are some crucial differences compared to those with hyperthyroidism. Clearly, low levels of THs affect several organs. First, there is reduced glucose absorption by the gastrointestinal tract. Decreased hepatic glucose output is observed due to diminished liver and muscle gluconeogenesis and glycogenolysis [37]. Regarding peripheral tissues, reduced insulin-stimulated glucose transport, glucose disposal, and utilization are observed in hypothyroid individuals due to insulin resistance [38]. The glucose oxidation rate and glycogen production are reduced as well. Insulin resistance, both fasting and postprandial, has been

detected in patients with subclinical and overt hypothyroidism [39]. Insulin resistance may be correlated with reduced expression of the GLUT4 transporter, elevated free fatty acids, and impaired leptin action.

Regarding beta cell function, glucose-induced insulin secretion is increased, and several studies have shown that insulin levels are elevated in hypothyroidism [40]. Furthermore, the half-life of insulin is prolonged due to reduced insulin clearance by the renal system [41]. In people who have DM and hypothyroidism and are treated with insulin, an adjustment in insulin dosage might be needed. Diminished renal insulin clearance leads to higher insulin levels; therefore, exogenously administered insulin requirements might be lower [42][43].

2.3. Thyroid Malignancies

The full spectrum of risk factors for TC is not well established. Environmental exposure to neck irradiation, inadequate iodine intake, family history of TC, and lifestyle factors are believed to be associated with the increase in prevalence [44][45][46][47][48][49]. The role of other risk factors in the development of TC must be clarified. Therefore, a possible causable role of T2DM and obesity in TC is considered. Yeo et al. performed a systematic review and meta-analysis to investigate the association between T2DM and the incidence of TC. Data from 13 studies were extracted, showing that T2DM was correlated with a notable increase in the risk of TC by approximately 20%. Furthermore, women with T2DM experienced a 30% higher risk of TC (1.38-fold increased risk) compared to their counterparts without DM, but this finding was not replicated in men [50].

The worldwide origin of the studies provided considerable population heterogeneity and indicated that the risk associated with DM was more prominent among women in areas with a high incidence of TC compared to other geographical areas [50]. Another more recent meta-analysis by Yin et al. investigated the association between TC and insulin resistance, metabolic syndrome, and its components. In accordance with the findings of the previous study, an increased incidence of TC was observed in women but not in men. Insulin resistance, dysglycemia, high body mass index (BMI), and hypertension were shown to significantly increase the incidence of TC. More particularly, insulin resistance has the highest risk estimate among components of the metabolic syndrome and is related particularly to PTC. There was a positive correlation with TC prevalence in both women and men with BMI > 25 kg/m^2, but this correlation was stronger in men [51]. On the contrary, a large prospective study [52] and a pooled analysis of five prospective studies [53] did not detect a significant association between DM and TC. A previous review of the literature indicated that any association between T2DM and TC is probably weak [54].

There are some suggestive molecular biological mechanisms that could explain the association between DM and the increase in the incidence of TC. First, hyperinsulinemia observed in patients with T2DM can impede cell apoptosis and promote cell proliferation through stimulation of insulin and the insulin-like growth factor-1 (IGF-1) pathway [55]. Increased insulin levels may affect TC risk, which is mediated by insulin receptors overexpressed in tumor cells and tissues [56]. In addition, insulin can play a key role in the promotion of thyroid carcinogenesis through the stimulation of mitogen-activated protein kinase (MAPK) and phosphatidylinositide 3-kinase pathways by mimicking IGF-1 and binding to the IGF-1 receptor [56]. Regarding stimulation of the IGF1 signaling pathway, hyperinsulinemia seen in T2DM reduces IGF-binding protein levels and enhances bioavailable IGF levels afterward. Therefore, a suggestive mechanism is that hyperinsulinemia directly increases cancer progression through overexpressed insulin receptors or indirectly through IGF-1 signaling [57].

Second, long-term exposure to higher TSH levels was correlated with an increased probability of DTC and a more aggressive tumor stage [58]. Elevated TSH levels are observed to be three times more frequent in people with T2DM compared to controls without DM [42]. Overproduction of THs promotes thyroid inflammation and TC through genomic and nongenomic effects. The genomic effect stimulates thyroid carcinogenesis through specific nuclear receptors; however, activation of the MAPK signaling pathway has been suggested to be involved in the pathogenesis of PTC. Furthermore, a novel pathway mediated by a membrane receptor located in integrin αVβ3 has been detected, which in part explains the proliferative and angiogenic effects of THs [59]. A different mechanism involves the impact of hyperglycemia on tumor cell growth and proliferation through increased pro-inflammatory and oxidative stress [54][60].

Glucose can increase the production of reactive oxygen species, especially nitric oxide [61]. Vitamin D deficiency is observed in 70% of individuals with DM [54] and, in this state, inactivation of deiodinase II leads to decreased glucose transporter 4 (GLUT4) transcription by skeletal muscle and adipose tissue, thus inducing insulin resistance and thyroid carcinogenesis [54][62]. In addition, in people living with obesity, adipocytokines and cytokines are secreted by adipocytes and inflammatory cells, respectively, infiltrating adipose tissue and contributing to the pathogenesis of insulin resistance. Adipocytokines are generally upregulated with increasing fat mass, in contrast with adiponectin, which is downregulated [63]. The most abundant and most investigated adipocytokines, leptin and adiponectin, may also be related to an increased incidence of TC. The increased levels of leptin that are observed in obesity are correlated with increased cancer

generation. Rehem et al. found that serum leptin levels in patients with DTC were higher and significantly decreased after thyroidectomy compared to prethyroidectomy levels [64]. Additionally, another study by Cheng et al. found that leptin and its receptor expression were positively associated with increased incidence and greater tumor size in patients with PTC [65].

Adiponectin acts as an insulin-sensitizing, anti-inflammatory, and anti-tumor agent, the latter by inhibiting cell proliferation and angiogenesis and increasing apoptosis. Low adiponectin levels observed in central obesity aggravate and are aggravated by insulin resistance, resulting in a vicious cycle with metabolic, inflammatory, and possibly oncogenic consequences [64][66]. Mitsiades et al. demonstrated that patients with TC had lower levels of circulating adiponectin than healthy controls. Therefore, circulating adiponectin is independently and inversely associated with the risk of TC [67].

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