Review Article

Prevalence And Association Of Thyroid Disorders With Diabetes Mellitus

ABSTRACT

Background: Diabetes mellitus and thyroid dysfunction are closely related. Numerous studies have reported an increased prevalence of thyroid disorders in diabetic patients, especially in type 1 diabetes mellitus.

Objectives: Therefore, the purpose of this review is to discuss the numerous underlying mechanisms behind the relationship between diabetes mellitus and thyroid dysfunction in order to demonstrate that the correlation between these two prevalent conditions is unlikely to be a coincidental finding.

Review: Diabetes and Thyroid disorders are characterized by endocrine system dysfunction. Thyroid hormones influence glucose metabolism in different ways, for example, they increase absorption of glucose from the gut, increase GLUT-2 level, regulate energy balance, and cause increased lipolysis which ultimately raises glucose levels in the body. Furthermore, thyroid hormones interact with adiponectin, leptin, ghrelin, to affect glucose metabolism. Additionally, studies suggest that hyperthyroidism impairs diabetic glycemic control, whereas hypothyroidism increases the risk of hypoglycemia, further complicating diabetes management.

Conclusion: This paper emphasizes thyroid abnormalities, if left untreated, can raise the risk of several diabetes complications including retinopathy, neuropathy, and nephropathy, and can worsen diabetic symptoms. As a result, treating subclinical hypothyroidism or hypothyroidism in diabetic individuals can be advantageous. Therefore, a systematic method for early thyroid testing in diabetic patients to avoid severe complications is highly recommended.

Keywords: Thyroid disorders, Diabetes mellitus, Thyroid hormones, Type 1 diabetes mellitus, Diabetes and Thyroid dysfunction

1. INTRODUCTION

The diabetes mellitus and thyroid disorders are the most frequently occurring chronic conditions with high prevalence rates among different populations. According to the research, in United States the prevalence of TD has been recorded 6.6 percent in adult population [1]. Similarly, another study reported higher prevalence of thyroid disorders in females compared to males. On the other hand, since 1980, the global prevalence of diabetes has nearly been doubled, increasing from 4.7 percent to 8.5 percent among adults [2]. According to a survey approximately 14% of the adult population in the United States suffers from either impaired fasting glucose levels.

Diabetes and thyroid disorders both have a prevalence rate, and these diseases typically coexist in the adult population. The NHANES III research has reported a higher prevalence of TD in united states among diabetic individuals than in non-diabetics, particularly in those with positive anti-thyroperoxidase (TPO) antibodies (Abs) [3]. Thyroid hormones play a role in carbohydrate metabolism and pancreatic function regulation, for example, hyperthyroidism (high levels of thyroid hormone) can impair the production, activity, and clearance of insulin, as well as several other aspects of carbohydrate metabolism, resulting in hyperglycemia. On the other hand, hypothyroidism (inadequate thyroid hormone) can also impair the metabolism and action of insulin, resulting in insulin resistance. The thyroid glands hyper and hypofunction affects carbohydrate metabolism at the level of pancreas: the islet cell and GLUT controlled glucose functions by posing crucial therapeutic and diagnostic complexities, as well as metabolizing biological cellular targets. Furthermore, diseases that are genetically and clinically linked affect islet and thyroidal cells [2]. While diabetes affects thyroid functioning in different ways. T2DM lowers thyroid-stimulating hormone levels and impairs the conversion of thyroxine (T4) to triiodothyronine (T3) in the peripheral tissues leading to different health issues including weight problems and muscle weakness. Poorly managed Type 2 diabetes can also cause hyperinsulinemia and insulin resistance resulting in increased thyroid tissue growth and nodules formation. This research emphasizes the importance of recognizing the interdependent relationship between diabetes and thyroid disorders which will aid medical professionals in deciding the best screening and treatment options for both conditions.

Comment [SJ1]: (TD)

Comment [SJ2]: Type 2 Diabetes Mellites (T2DM)

2. THE PREVALENCE OF THYROID ABNORMALITIES IN DIABETIC PATIENTS AND GENERAL PUBLIC

Thyroid diseases affect a large percentage of the population. According to the 1970 Whickham research, conducted in northern England showed 6.6 percent of the general adult population had thyroid dysfunction. [4]. Another survey of 17,353 people in the NHANES III research revealed that 4.6 percent of people had hypothyroidism and 1.3 percent had hyperthyroidism [5]. Similarly, another research revealed that thyroid illness was more common in women than in males, and in diabetics than in nondiabetics.

Thyroid dysfunction is more common among diabetics than in the general population. According to Perros et al., diabetics had a 13.4% prevalence of thyroid illness, with the lowest prevalence of 6.9% in type 2 male diabetics and the highest prevalence of 31.4 percent in type 1 females diabetics [6]. Similarly, recent researches have shown that approximately 12.3 percent of Greek diabetic patients [7] had thyroid dysfunction. On the other hand, another study revealed that 16 percent of Saudi type 2 diabetic patients had thyroid dysfunction [8]. Additionally, thyroid dysfunction was shown to be prevalent in 12.5 percent of type 2 diabetes patients in Jordan. Furthermore, GADA-positive individuals have a 3.5-fold greater incidence of autoimmune thyroiditis [9].

Researches have also revealed that thyroid issues frequently occurred in people with type 1 diabetes compared to type 2 diabetic patients. According to cross-sectional research in approximately 1419 type 1 diabetic children thyroid dysfunction was discovered. Hashimoto's thyroiditis was found in 3.5 percent of the participants [10]. Additionally, researches have shown that positive TPO antibodies were found in 38% of diabetic individuals, and this has been proven to predict the development of subclinical and clinical hypothyroidism. Recently Ghawil et al. reported that 7% of type 1 diabetic Libyans had positive TG antibodies whereas 23.4 percent of type 1 diabetic Libyans had positive TPO antibodies [11]. The connection between T1DM and AITD has been identified as APS3 variation, which is a variety of APS3. Similarly, researchers have also found four genes; FOXP3 genes CTLA-4, HLA, and PTPN22 can be responsible for the coexistence of the thyroid disorders and diabetes.

3. THYROID HORMONE EFFECTS ON GLUCOSE HOMEOSTASIS

Thyroid hormones influence glucose metabolism in a variety of ways. Hyperthyroidism has been linked to an increase in blood sugar levels [12]. The insulin half-life is shortened in

hyperthyroidism, resulting in the production of physiologically inactive insulin precursors [13]. According to research by Bech et al, proinsulin levels rose in Graves' illness in response to a meal [14]. Furthermore, unmanaged hyperthyroidism was linked to a lower C-peptide to proinsulin ratio, implying a proinsulin processing defect [15]. The increase in glucose gut absorption interceded by excess thyroid hormones is another mechanism that explains the link between hyperthyroidism and hyperglycemia.

Hyperthyroidism increases endogenous glucose production through different mechanism. Thyroid hormones induce GLUT2 concentrations in hepatocyte plasma membranes to rise. Because GLUT2 is the primary glucose transporter in the liver, increased GLUT-2 levels can lead to an increase in hepatic glucose output and abnormal glucose metabolism. Additionally, hyperthyroidism induces lipolysis, leading to increased FFA, thereby accelerating gluconeogenesis in the liver. The increase in catecholamine-induced lipolysis caused by elevated thyroid hormone levels may account for the rise in FFA generation. Moreover, hyperthyroidism causes an increase in non-oxidative glucose disposal, which leads to excessive production of lactate, entering Cori cycle and stimulating glucose production in the liver. Furthermore, hyperthyroidism causes an increase in catecholamine, GH and glucagon, levels, which results in impaired glucose tolerance.

Diabetes patients with hyperthyroidism show worsen glycemic control, and thyrotoxicosis can cause diabetic ketoacidosis in diabetic individuals [16]. Hypothyroidism affects glucose metabolism in different ways. For example, hepatic glucose production decreases in hypothyroidism [17], which explains the decreased insulin demand in hypothyroid diabetes patients. In research done by Leong et al, it was discovered that recurrent hypoglycemia episodes are indicators of hypothyroidism in type 1 diabetic individuals, and thyroid hormone supplementation can decrease blood glucose fluctuations [18]. A case-control study conducted in patients with type 1 diabetes reported that individuals with subclinical hypothyroidism had more hypoglycemic episodes in the 12 months indicated that diagnosis of hypothyroidism was more common in diabetes than euthyroid. On the other hand, clinical and subclinical hypothyroidism, have been labeled as insulin resistant states. Additionally, according to in vivo and invitro investigations, this is attributed to decreased insulin-induced glucose consumption in peripheral tissues. Recent research including people from a Chinese community also found that patients with metabolic syndrome had a greater TSH level than those who did not have metabolic syndrome, indicating that subclinical hypothyroidism can increase the risk of metabolic syndrome [19]. Researcher Erdogan et al. has discovered that subclinical and overt hypothyroidism patients had a higher rate of metabolic syndrome than healthy controls [20]. As a result, it appears that hypothyroidism should be considered in

patients newly diagnosed with metabolic syndrome. This leads to a question of whether routine thyroid disease screening can be a cost-effective technique in all newly diagnosed persons with metabolic syndrome. The higher risk of nephropathy in individuals suffering from type 2 diabetes having subclinical hypothyroidism can be explained by the increased peripheral vascular resistance and decreased cardiac output seen with hypothyroidism, as well as the accompanying decrease in glomerular filtration rate and renal flow. According to Den Hollander et al. in 2005, treatment of hypothyroidism enhanced renal function in diabetic individuals [21]. Yang et al. discovered that cases of severe retinopathy were more observed in diabetic patients having subclinical hypothyroidism than euthyroid diabetic patients. This higher risk of nephropathy and retinopathy in diabetic patients with subclinical hypothyroidism suggests that type 2 diabetic patients should be screened for thyroid abnormalities and treated accordingly.

4. THYROID HORMONES, ADIPONECTIN, LEPTIN, AND GHRELIN

Thyroid hormones, in combination with adipocytokines and gut hormones, may influence carbohydrate mechanisms. Adiponectin, the most abundant adipokine secreted by adipose tissue and with important insulin-sensitizing properties is the most abundant of these adipocytokines. Decreased levels of adiponectin have long been linked to an increased risk of type 2 diabetes. Thyroid hormones and adiponectin have several biological features, including the potential to decrease body fat by boosting lipid oxidation and thermogenesis. Adiponectin's association with the gC1q receptor, typically present in thyroid mitochondria, has been suggested to influence thyroid hormone production [22]. T3, on the other hand, has been shown to inhibit adiponectin mRNA expression in rat models, particularly in white adipose tissue. The connection between adiponectin and thyroid hormones is still unclear, and the few studies that have looked into it have provided mixed results. Several researchers reported higher adiponectin levels in hyperthyroidism while others found that its levels remain unchanged even in the presence of excessive thyroid hormones. Dimitriadis et al. demonstrated lower adiponectin levels in hypothyroidism, and Nagasaki et al. discovered that both control group and hypothyroid patients had comparable levels of adiponectin. As a result, no definitive conclusion can be reached at this time, and more research is needed to resolve the aforementioned issues.

Adipocytes also generate leptin, a hormone that controls energy expenditure and body weight. Several studies have discovered a link between leptin and thyroid hormones. However, the outcomes are unclear. In hyperthyroidism, some studies indicated a drop in leptin levels, whereas others found no change. In hypothyroid individuals, higher, stable, and even reduced amounts of leptin have been discovered. Hypothyroid dogs have been shown to have higher levels of blood leptin and insulin. Leptin, on the other hand, may enhance

circulation T3 levels by boosting the type I iodothyronine 5′-deiodinase enzyme activity. The outcomes of thyroid dysfunction and leptin are complicated by changes in fat accumulation that accompany thyroid disorders. The complicated interaction between leptin and thyroid hormones as well as its prospective impact on glucose metabolism is yet unknown.

Ghrelin is an orexigen that is secreted by the stomach fundus. Ghrelin has been linked to a number of diabetogenic effects, including a reduction in the production of the insulin-sensitizing hormone adiponectin [23]. Ghrelin circulates in major two forms: deacylated and acylated ghrelin with deacylated ghrelin being the more common circulating type. Ghrelin levels tend to be reduced in obese people, and it has been linked to hyperinsulinemia in people with type 2 diabetes [24]. Ghrelin levels were shown to be lower in hyperthyroid individuals, but these levels returned to normal once hyperthyroidism was treated pharmacologically. Because hyperthyroidism is negatively associated with energy balance, therefore ghrelin levels should rise. In thyroid dysfunction situations, ghrelin levels appear to be linked to insulin resistance instead of energy balance and food consumption. Insulin resistance is connected to hyperthyroidism, and hyperinsulinemia regulates ghrelin levels [25]. Ghrelin levels have been discovered to be higher in hypothyroid individuals, but these levels have been found to be restored with L-thyroxine therapy.

Caminos et al. [26] found increased circulatory ghrelin and stomach ghrelin mRNA levels in hypothyroid rat models. Hypothyroid individuals were shown to have ghrelin levels that were equivalent to healthy people in previous trials, and these levels did not alter appreciably following thyroid hormone replacement [27]. As a result, a limited number of researches examining the relationship between adipokines, ghrelin, and thyroid dysfunction have provided mixed results. For example, individual characteristics differences alternations in energy expenditure and fat mass associated with hypo or hyperthyroidism, assays variability used for hormonal measures particularly for measuring ghrelin and degree and length of thyroid dysfunction, can all explain the inconsistencies. Furthermore, ghrelin is found in two different forms, as previously stated. Food intake is stimulated by acyl ghrelin, while food intake is reduced by desacyl ghrelin, resulting in a negative energy balance. Confounding findings can be obtained by measuring either form or total ghrelin.

5. Energy Expenditure And Thyroid Function

Thyroid hormones influence glucose metabolism indirectly by modulating energy balance. Although the underlying processes are unknown, these hormones have been demonstrated

to change the production of uncoupling proteins in brown adipose tissue, which is important for successful thermoregulation.

Thyroid hormones and TRH have recently been discovered to have a function in the core regulatory pathways for thermogenesis. Type 4 melanocortin receptor (MC4R) and Thyroid hormone nuclear receptors (TRs) are expressed by TRH neurons in the hypothalamus, with the latter being a critical receptor implicated in central energy control. Activation of the MC4R gene increases energy expenditure and decreases food intake all of which inactivates the MC4R mutations linked to obesity. T3's inhibitory action on MC4R expression aids in energy conservation in hyperthyroid conditions. The arcuate nucleus's AgRP (Agouti-related protein) and POMC (pro) neurons both operate on the MC4R. T3 has been discovered to reduce the hypothalamic sensitivity of the AgRP and POMC signaling by lowering the expression of MC4R.

In the hypothalamus, AMP-activated protein kinase (AMPK), known as a cellular energy sensor, facilitates the effects of numerous hormonal and dietary inputs. Obesity occurred in mice without AMPK2 in POMC neurons due to a slower resting metabolic rate and poor food management. On the other hand, AMPK2 mutant mice in AgRP neurons, remained slender and had increased sensitivity to melanocortin agonists [28]. Injecting an adenovirus expressing the dominant-negative version of “AMPK” (Ad-DN AMPK) into the hypothalamus of male rats caused considerable reductions in glucose production. According to López et al, hyperthyroidism or central T3 injection decreased hypothalamus AMPK activity. As a result of their interplay with numerous hypothalamic signals, thyroid hormones may have an indirect effect on glucose metabolism. However, the precise processes behind this intricate connection are still being investigated.

6. THE INFLUENCE OF DIABETES MELLITUS ON THYROID HORMONES AND THYROID DISORDERS

Thyroid hormones have been found to be altered in diabetic individuals, particularly in persons with poor glycemic control. Studies have shown that nocturnal TSH peak can be eliminated or attenuated in diabetes individuals, and the TSH response to TRH might be defective. Uncontrolled diabetic individuals have been found to have lower T3 levels. This "low T3 condition" might be explained by a problem with peripheral T4 to T3 conversion, which improves with better glycemic management. Coiro et colleagues reported that the normal nocturnal TSH peak was not improved by glycemic control in type 1 diabetes patients with missing residual pancreatic beta-cell activity, indicating a diabetes-dependent modification in the central regulation of TSH. Higher levels of circulating insulin have been linked to insulin resistance ultimately causing a proliferative impact on thyroid tissue, further

resulting in increased thyroid size and nodule development [29]. Additionally, patients with Grave's orbitopathy have a greater frequency of type 1 diabetes than the general population. The optic nerve becomes more sensitive to pressure as a result of the vasculopathy alterations linked with diabetes. The expanded additional ocular muscles provide pressure. As a result, diabetic people with Graves ophthalmopathy had a greater frequency of dysthyroid optic neuropathy than nondiabetic ones.

7. THYROID DISORDERS PREVALENCE

Thyroid disorders are more prevalent among diabetic patients. According to the statement of general prevalence, approximately 6% of a randomized sample population has some form of thyroid disorder. However, in the diabetic subset of the population sample, the prevalence of diagnosed thyroid pathology rises by 10%. Moreover, thyroid autoimmune disorders are more prevalent in Type 1 diabetic patients. According to studies, up to 30% of Type 1 diabetic individuals had autoimmune thyroid disease in some form. When compared to a healthy sample, the prevalence of postpartum thyroiditis in diabetic patients is three times higher. Thyroid disorders were found to be more common in type 2 diabetic patients than in the general population. Additionally thyroid disorders are the second most common disorder in the United States, affecting approximately 27 million people, with up to half of these people going undiagnosed. As a result of the substantial overlap between the two groups, there is a higher probability of persons being impacted by both thyroid and diabetes illness at the same time. According to studies, almost 4 million people in the United States have hypothyroid and get thyroxine replacement medication each year. Hyperthyroidism, on the other hand, is less frequent, with a 9:1 female-to-male ratio. Grave's disease is known to affect mostly young adults, whereas toxic multinodular goiters are known to attack older people [30].

8.CONCLUSION

The relationship between diabetes and thyroid disorders is complicated and interdependent. The thyroid gland is important for metabolic regulation and has a significant impact on diabetes management and clinical outcomes. Thyroid abnormalities, if left untreated, can raise the risk of several diabetes complications and modify the processes that cause diabetic symptoms. In individuals with Graves' illness, insulin resistance may exacerbate thyroid gland nodularity, and associated diabetes can increase vision loss risk. Furthermore, hyperthyroidism affects diabetic glycemic control, whereas hypothyroidism increases the risk

of hypoglycemia, complicating overall diabetes treatment. Thyroid hormones interact with adiponectin, leptin, and gut hormones, including ghrelin, to affect glucose metabolism further. As a result, this link and the consequent change in metabolic effects need to be investigated further. Moreover, thyroid dysfunction has been discovered to be more prevalent in patients with diabetes, particularly type 1 diabetes. Thyroid dysfunction that is undiagnosed has a significant influence on diabetes and its consequences. Additionally, diabetic individuals with subclinical hypothyroidism had a greater prevalence of retinopathy and nephropathy, as well as more severe nephropathy. As a result, treating subclinical hypothyroidism in diabetic individuals may be advantageous. Thyroid dysfunction can be easily detected with hematological laboratory tests, and it can be treated well. As a result, screening for thyroid abnormalities on a regular basis in diabetes patients is indicated. Moreover, the systematic approaches of thyroid testing in diabetes people are found to be beneficial. Although no concrete standards for thyroid dysfunction screening in diabetes patients exist at this time, judicious service from healthcare professionals for the coexistence of both diseases has the potential to improve the quality of health care available.

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