Reviewer Article
Thyroid Disorders and Diabetes Mellitus

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Received 26 January 2011; Accepted 13 May 2011

Academic Editor: Juan Bernal

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Studies have found that diabetes and thyroid disorders tend to coexist in patients. Both conditions involve a dysfunction of the endocrine system. Thyroid disorders can have a major impact on glucose control, and untreated thyroid disorders affect the management of diabetes in patients. Consequently, a systematic approach to thyroid testing in patients with diabetes is recommended.

1. Introduction
Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported [1, 2]. On one hand, thyroid hormones contribute to the regulation of carbohydrate metabolism and pancreatic function, and on the other hand, diabetes affects thyroid function tests to variable extents. This paper demonstrates the importance of recognition of this interdependent relationship between thyroid disease and diabetes which in turn will help guide clinicians on the optimal screening and management of these conditions.

2. Frequency of Thyroid Disorders in the General Population and in Patients with Diabetes
Thyroid disorders are widely common with variable prevalence among the different populations. Data from the Whickham survey conducted in the late 1970s in the north of England revealed a prevalence of 6.6% of thyroid dysfunction in the adult general population [3]. In the Colorado Thyroid Disease Prevalence study involving 25,862 participants attending a state health fair, 9.5% of the studied population were found to have an elevated TSH, while 2.2% had a low TSH [4]. In the NHANES III study, a survey of 17,353 subjects representing the US population, hypothyroidism was found in 4.6% and hyperthyroidism in 1.3% of subjects [5]. The latter further observed an increased frequency of thyroid dysfunction with advancing age and a higher prevalence of thyroid disease in women compared to men and in diabetic subjects compared to nondiabetic.

Several reports documented a higher than normal prevalence of thyroid dysfunction in the diabetic population. Particularly, Perros et al. demonstrated an overall prevalence of 13.4% of thyroid diseases in diabetics with the highest prevalence in type 1 female diabetics (31.4%) and lowest prevalence in type 2 male diabetics (6.9%) [6]. Recently, a prevalence of 12.3% was reported among Greek diabetic patients [7] and 16% of Saudi patients with type 2 diabetes were found to have thyroid dysfunction [8]. In Jordan, a study reported that thyroid dysfunction was present in 12.5% of type 2 diabetic patients [9]. However, thyroid disorders were found to be more common in subjects with type 1 diabetes compared to those with type 2 diabetes. Additionally, a 3.5-fold increased risk of autoimmune thyroiditis was noticed in GADA positive patients [10]. Thyroid disorders remain the most frequent autoimmune disorders associated with type 1 diabetes. This was shown in a cross-sectional study involving 1419 children with type 1 diabetes mellitus, where 3.5% had Hashimoto’s thyroiditis [11]. In addition, positive TPO antibodies have been reported in as high as 38% of diabetic individuals and have been...
shown to be predictive for the development of clinical and subclinical hypothyroidism [12–14]. Very recently, Ghawil et al. documented that 23.4% of type 1 diabetic Libyan subjects had positive TPO antibodies and 7% had positive TG antibodies [15]. The association betweenAITD and T1DM has been recognized as a variant of APS3 referred to as APS3 variant [16]. Common susceptibility genes have been acknowledged to confer a risk for development of bothAITD and type 1 diabetes mellitus. Currently, at least four shared genes have been identified including HLA [17–22], CTLA-4 [23], PTPN22 [24, 25], and FOXP3 genes [26].

3. Effects of Thyroid Hormones on Glucose Homeostasis

Thyroid hormones affect glucose metabolism via several mechanisms. Hyperthyroidism has long been recognized to promote hyperglycemia [27]. During hyperthyroidism, the half-life of insulin is reduced most likely secondary to an increased rate of degradation and an enhanced release of biologically inactive insulin precursors [28, 29].

In untreated Graves’ disease, increased proinsulin levels in response to a meal were observed in a study by Bech et al. [30]. In addition, untreated hyperthyroidism was associated with a reduced C-peptide to proinsulin ratio suggesting an underlying defect in proinsulin processing [31]. Another mechanism explaining the relationship between hyperthyroidism and hyperglycemia is the increase in glucose gut absorption mediated by the excess thyroid hormones [32, 33].

Endogenous production of glucose is also enhanced in hyperthyroidism via several mechanisms. Thyroid hormones produce an increase in the hepatocyte plasma membrane concentrations of GLUT2 which is the main glucose transporter in the liver, and consequently, the increased levels of GLUT-2 contribute to the increased hepatic glucose output and abnormal glucose metabolism [34, 35]. Additionally, increased lipolysis is observed in hyperthyroidism resulting in an increase in FFA that stimulates hepatic gluconeogenesis. The increased release of FFA could partially be explained by an enhanced catecholamine-stimulated lipolysis induced by the excess thyroid hormones [36]. Moreover, the nonoxidative glucose disposal in hyperthyroidism is enhanced resulting in an overproduction of lactate that enters the Cori cycle and promotes further hepatic gluconeogenesis. The increase in GH, glucagon and catecholamine levels associated with hyperthyroidism further contributes to the impaired glucose tolerance [37–39].

It is well known that diabetic patients with hyperthyroidism experience worsening of their glycemic control and thyrotoxicosis has been shown to precipitate diabetic ketoacidosis in subjects with diabetes [40, 41].

As for hypothyroidism, glucose metabolism is affected as well via several mechanisms. A reduced rate of liver glucose production is observed in hypothyroidism [42] and accounts for the decrease in insulin requirement in hypothyroid diabetic patients. Recurrent hypoglycemic episodes are the presenting signs for the development of hypothyroidism in patients with type 1 diabetes and replacement with thyroid hormones reduced the fluctuations in blood glucose levels as demonstrated by Leong et al. [43]. In a case control study involving type 1 diabetic patients, those with subclinical hypothyroidism experienced more frequent episodes of hypoglycemia during the 12 months prior to the diagnosis of hypothyroidism compared to euthyroid diabetics. On the other hand, both clinical and subclinical hypothyroidisms have been recognized as insulin resistant states [44–46]. In vivo and in vitro studies have shown that this is due to impaired insulin stimulated glucose utilization in peripheral tissues [44, 45, 47, 48]. A recent study involving subjects from a Chinese population found a higher TSH level in patients with metabolic syndrome compared to that in the nonmetabolic syndrome group suggesting that subclinical hypothyroidism may be a risk factor for metabolic syndrome [49]. More recently, Erdogan et al. found an increased frequency of metabolic syndrome in subclinical and overt hypothyroidism compared to healthy controls [50]. Therefore, it seems prudent to consider hypothyroidism in newly diagnosed metabolic syndrome patients. This raises the issue whether routine screening for thyroid disease in all patients newly diagnosed with metabolic syndrome will be cost effective. Furthermore, an increased risk of nephropathy was shown in type 2 diabetic patients with subclinical hypothyroidism [51] which could be explained by the decrease in cardiac output and increase in peripheral vascular resistance seen with hypothyroidism and the resulting decrease in renal flow and glomerular filtration rate [52]. In 2005, Den Hollander et al. reported that treating hypothyroidism improved renal function in diabetic patients [53]. As for retinopathy, Yang et al. demonstrated recently that diabetic patients with subclinical hypothyroidism have more severe retinopathy than euthyroid patients with diabetes [54].

The increased risk of retinopathy and nephropathy observed in diabetic patients with subclinical hypothyroidism provides evidence in favor of screening patients with type 2 diabetes for thyroid dysfunction and treating when present.

4. Leptin, Adiponectin, Ghrelin, and Thyroid Hormones

Thyroid hormones may influence carbohydrate mechanisms via its interaction with adipokines and gut hormones. Among these adipokines, adiponectin is the most abundant adipokine secreted by the adipose tissue and has important insulin-sensitizing properties. Low levels of adiponectin have been shown to confer a higher risk for development of type 2 diabetes. Adiponectin and thyroid hormones share some biological properties including reduction in body fat by increasing thermogenesis and lipid oxidation [55]. It has been suggested that adiponectin might influence thyroid hormone production through its interaction with Gc1q receptor found in thyroid mitochondria [56]. On the other hand, it was recently shown that T3 exhibited an inhibitory effect in rat models on adiponectin mRNA expression particularly on white adipose tissue [57]. The relationship between thyroid hormones and adiponectin remains to be
clarified and limited studies addressing this issue have shown inconsistent results. Some studies found that adiponectin are increased in hyperthyroidism [58–60], whereas other studies report unchanged levels in states of excess thyroid hormones [61, 62]. In hypothyroidism, reduced levels of adiponectin have been shown by Dimitriadis et al. [44], and comparable levels of adiponectin were observed in hypothyroid patients and controls in a study by Nagasaki et al. [63]. Therefore, no definite conclusion can yet be drawn, and further studies are needed to clarify the above controversies.

Leptin is another hormone produced by adipocytes that regulates energy expenditure and body weight. A correlation between leptin and thyroid hormones has been demonstrated in several studies. However, results have also been discordant. Some studies showed a decrease in leptin levels in hyperthyroidism [61, 64], whereas others observed unchanged levels [65–67]. Similarly, increased [64, 67], unchange [66], and even decreased [65] values of leptin have been reported in hypothyroid patients. An increase in serum leptin and insulin have been described in hypothyroid dogs [68]. On the other hand, leptin, by enhancing the activity of type I iodothyronine 5′-deiodinase enzyme, could result in an increase in circulating T3 level [69]. The changes in fat mass accompanying thyroid diseases complicates the interpretation of the results of studies on leptin and thyroid dysfunction. However, the complex interplay between thyroid hormones and leptin and its possible influence on carbohydrate metabolism remains to be elucidated.

Ghrelin is an orexigen secreted from the fundus of the stomach. It has been shown to exert several diabetogenic effects including decreasing secretion of the insulin sensitizing hormone adiponectin [70]. In addition, ghrelin circulates in two different forms acylated and desacylated ghrelin with the latter constituting the major circulating form. Ghrelin levels are lower in obese subjects and those with type 2 diabetes, states associated with hyperinsulinemia [71]. Reduced ghrelin levels were observed in hyperthyroid patients [72, 73], and these levels rose to normal values after pharmacological treatment of hyperthyroidism [74–76]. Hyperthyroidism, being a state of negative energy balance should result in an increase in ghrelin levels. Interestingly, ghrelin levels in thyroid dysfunction states seem to correlate with insulin resistance rather than food intake and energy balance [77]. Hyperthyroidism is associated with insulin resistance [77] and hyperinsulinemia suppresses ghrelin levels [78]. Increased levels of ghrelin has been observed in hypothyroid patients, and these levels normalized with L-thyroxine treatment [74, 79].

In hypothyroid rat models, increased circulating ghrelin and gastric ghrelin mRNA levels were demonstrated by Caminos et al. [80]. However, in other studies, hypothyroid patients were reported to have comparable ghrelin levels to that of healthy subjects and those levels were not significantly altered after thyroid hormone replacement [77, 81, 82]. Therefore, the limited number of studies assessing the link between thyroid dysfunction, on one hand, and ghrelin and adipokines, on the other hand, have yielded conflicting results. These discrepancies could be potentially explained by differences in individuals’ characteristics, changes in fat mass and energy expenditure accompanying hyper- or hypothyroidism, duration and degree of thyroid dysfunction, and variability in the assays used for hormonal measurements particularly for ghrelin. As previously mentioned, ghrelin circulates in two major forms, acyl ghrelin which exerts a stimulatory effect on food intake and desacyl ghrelin which reduces food intake inducing a state of negative energy balance. Measuring either form or measuring total ghrelin will lead to confounding results.

5. Thyroid Function and Energy Expenditure

Besides all of the above described mechanisms, thyroid hormones can indirectly affect glucose metabolism through modulation of energy homeostasis. Although the underlying mechanisms have not yet been clearly defined, thyroid hormones have been shown to alter the expression of uncoupling proteins in brown adipose tissue involved in effective thermoregulation [83].

More recently, a role for thyroid hormones and TRH in the central regulatory pathways for thermogenesis has been identified. TRH neurons in the hypothalamus express both thyroid hormone nuclear receptors (TRs) and type 4 melanocortin receptor (MC4R), a key receptor involved in central energy regulation [84]. Activation of MC4R reduces food intake and increases energy expenditure and inactivating mutations in MC4R are associated with obesity [85]. The repressive effect of T3 on the expression of MC4R helps in conserving energy in hyperthyroid states [86]. Furthermore, both the POMC (pro) and AgRP (Agouti-related protein) neurons of the arcuate nucleus act at the Mc4R. Thus, T3, by reducing the expression of MC4R, has been shown to decrease the hypothalamic sensitivity of the POMC and AgRP signaling [86].

AMP-activated protein kinase (AMPK), a cellular energy sensor, mediates the effects of various nutritional and hormonal signals in the hypothalamus.

Mice lacking AMPKα2 in POMC neurons developed obesity due to a reduced resting metabolite rate and a defective nutrient handling. On the other hand, AMPKα2 knockout mice in AgRP (Agouti-related protein) neurons of the arcuate nucleus developed lean with an enhanced sensitivity to melanocortin agonists [87]. On the other hand, injecting an adenovirus expressing the dominant-negative form of AMPK (Ad-DN AMPK) into the hypothalamus of male rats resulted in significant decrements in glucose production. Recently, López et al. showed that hyperthyroidism or central administration of T3 reduced the activity of hypothalamic AMPK [88]. Consequently, thyroid hormones could indirectly alter glucose metabolism via their interaction with various hypothalamic signals. However, the exact mechanisms behind this complex interaction remains to be clarified.

6. Effects of Diabetes Mellitus on Thyroid Hormones and Thyroid Diseases

Altered thyroid hormones have been described in patients with diabetes especially those with poor glycemic control. In diabetic patients, the nocturnal TSH peak is blunted
or abolished, and the TSH response to TRH is impaired [89]. Reduced T3 levels have been observed in uncontrolled diabetic patients. This “low T3 state” could be explained by an impairment in peripheral conversion of T4 to T3 that normalizes with improvement in glycemic control. However, in a study by Coiro et al. involving type 1 diabetes patients with absent residual pancreatic beta cell function, an amelioration in glycemic control did not restore the normal nocturnal TSH peak suggesting a diabetes-dependent alteration in the central control of TSH [90]. Higher levels of circulating insulin associated with insulin resistance have shown a proliferative effect on thyroid tissue resulting in larger thyroid size with increased formation of nodules [91, 92]. A higher prevalence of type 1 diabetes is observed in patients with Grave’s orbitopathy than in the normal population. Furthermore, the vasculopathic changes associated with diabetes renders the optic nerve more susceptible to the pressure exerted by the enlarged extraocular muscles. Consequently, a higher incidence of dysthyroid optic neuropathy is observed in diabetic subjects with Graves ophthalmopathy compared to nondiabetic [93].

7. Conclusion

The relationship between thyroid disorders and diabetes mellitus is characterized by a complex interdependent interaction. Insulin resistance states may increase thyroid gland nodularity and coexisting diabetes may increase risk of visual loss in patients with Graves’ disease. Hyperthyroidism impairs glycemic control in diabetic subjects, while hypothyroidism may increase susceptibility to hypoglycemias thus complicating diabetes management. Additionally, thyroid hormones may further alter carbohydrate metabolism via its interaction with leptin, adiponectin, and gut hormones, namely, ghrelin. However, this association and the resulting alteration in metabolic effects need further research. It has been shown that thyroid dysfunctions are more prevalent in people with diabetes and particularly type 1 diabetes. Furthermore, it seems that unidentified thyroid dysfunction could negatively impact diabetes and its complications. A higher frequency of retinopathy and nephropathy was observed in diabetic patients with subclinical hypothyroidism, and more severe retinopathy was noted as well. Therefore, management of subclinical hypothyroidism in patients with diabetes may prove beneficial. We conclude that a systematic approach to thyroid testing in diabetic subjects is favorable; however, no definitive guidelines exist regarding screening for thyroid dysfunction in diabetic patients. Finally, whether all patients with diabetes should be screened for thyroid function or whether patients with subclinical thyroid disease should be treated merits reconsideration.

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