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Association of Diabetes Mellitus and Thyroid Disorders: A Metabolic Prospective

Manish Mishra*, Mignonette Relatado-Sotto, Raju Panta, Miguel Miyares, Ranjan Solanki

Trinity School of Medicine, Ratho Mill, St. Vincent and the Grenadines, West Indies

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ABSTRACT

The prevalence of diabetes has nearly doubled since 1980, mounting from 4.7% to 8.5% in overall adult population. Thyroid disorder is another common endocrine disorder with prevalence of hypothyroidism as much as 4.6% and hyperthyroidism as much as 1.3% in population according to the National Health and Nutrition Examination Survey. These two most common endocrinopathies often co-exist and mutually influence each other. They have complex links of abnormal biochemical pathways, unregulated genetic expression of many genes and hormonal malfunctions. Thyroid hormones affects the regulation of carbohydrate metabolism, lipid metabolism and pancreatic function, and on the other hand, diabetes affects thyroid function tests to variable extents. In this review article we emphasized the epidemiology of diabetes and thyroid disorders, classification of thyroidism, and finally the impact of thyroidism to the various aspects of glucose and lipid metabolism in diabetics.

Keywords: Hyperthyroidism, Hypothyroidism, Euthyroidism, Subclinical Hypothyroidism, Type 1 Diabetes Mellitus, Type 2 diabetes mellitus.

Introduction

Diabetes mellitus (DM) and thyroid disorders (TD) are the two most common endocrine disorders, which often co-exist and mutually influence each other. A large number of studies have reported the association between DM and TD [1-5], and evidenced a range of complex links between biochemical, genetic and hormonal malfunction sex planning their patho-physiological association [5-7]. In 1927, Coller and Huggins proved the association of hyperthyroidism and deterioration of diabetes and found that the subtotal thyroidectomy improves glucose tolerance in patients with hyperthyroidism with coexisting diabetes [8]. The role of autoimmunity in the progression of TD has been observed among the people with type 1 diabetes mellitus (T1DM) and autoimmune thyroid disease [9].

**Correspondence*
Manish Mishra
Trinity School of Medicine, Ratho Mill, St. Vincent and the Grenadines, West Indies
E Mail: nmcmanish@gmail.com

A relationship between thyroid dysfunction and type 2 diabetes mellitus (T2DM) has also been suggested, but the possible underlying mechanisms are complicated [10]. The most probable mechanism for development of T2DM in patients with thyroid dysfunction could be due to disturbed genetic expression of many genes along with physiological abnormalities leading to impaired glucose utilization by the muscles, increased hepatic glucose output, and increased glucose absorption from intestine [5]. These endocrinopathies impact each other in various ways. Thyroid hormones (TH) contribute to the regulation of carbohydrate metabolism and pancreatic function, and on the contrary, diabetes affects thyroid function tests to variable extents [4]. Altered plasma triiodothyronine (T3) and thyroxine (T4) levels have been observed in diabetic patients with poor glycemic control [11]. To understand the interaction of DM and TD, the association of Hashimoto's thyroiditis (Hypothyroidism) and Graves' disease (thyroid over-activity) has been investigated in reference to DM. The importance of hyperinsulinemia/insulin resistance, in thyroid cell proliferation, which manifested as increased thyroid volume and nodule have been also observed [12-14].

Epidemiology

An estimated 422 million adults were living with diabetes in 2014 worldwide, as compared to 108 million in 1980. The over-all prevalence of diabetes has nearly doubled since 1980, escalating from 4.7% to 8.5% in the adult population. In last decade, diabetes prevalence has increased more rapidly in low and middle-income countries than in high-income countries [15-16].

As per 2017, National Diabetes Statistics Report, 30.3 million Americans (9.4% of the population), had diabetes in 2015. Out of the 29.1 million, 23.1 million were diagnosed and 7.2 million were undiagnosed. The highest proportion of diabetes (diagnosed and undiagnosed), 25.2% (in total 12 million), still belongs to the Americans at par the age of 65. As per estimation in 2015, 84.1 million Americans (33.9%) adults with age 18 and older had prediabetes [17-18].

Thyroid disorder is another common endocrinopathy with variable prevalence [1]. Wang and Crapo in 1997 mentioned that as many as 50% of people in the community have microscopic nodules, 3.5% have occult papillary carcinoma, 15% have palpable goiters, 10% exhibit an abnormal thyroid-stimulating hormone (TSH) level and 5% of women have overt hypothyroidism or hyperthyroidism [19].

Long back in 1977, Wickham survey reveals that the prevalence of thyroid dysfunction in male adults in England was 6.6% [20]. According to Colorado prevalence study, 9.5% of participants were found to have elevated TSH, while 2.2% had a low TSH [2]. According to the National Health and Nutrition Examination Survey (NHANES III Study), hypothyroidism and hyperthyroidism were reported in 4.6% and 1.3% of the total participants, respectively [21].

As per Framingham study, the observed prevalence of thyroid deficiency was 4.4%, evidenced by elevated serum TSH level in unselected population of elderly men and women (overt 60 years of age). The observed prevalence of thyroid deficiency in women was 5.9% more than men which was 2.3% [22]. As per NHANES III Study, the percentage of subjects with high serum thyroperoxidase antibodies (TPOAb) and thyroglobulin antibodies (TGAb) concentrations increases with age in both men and women [21]. The high concentrations of TPOAb and TGAb were more prevalent in women than in men and less predominant in blacks than in other ethnic groups [21]. As per Perros *et al*., the prevalence of thyroid dysfunction is increasing with age all over the world, and the frequency of prevalence was higher in women than men [23].The prevalence of palpable thyroid nodules in two non-biased population based studies, Framingham and Whickham, was 4.2 and 3.2%, respectively [20, 23, 24]. In Germany, thyroid nodules or goiter were found in 33% of 96,278 working adults aged 18-65 years screened by an ultrasound scan [25].

The overall prevalence of thyroid disease in diabetics was reported to be 13.4%, and was highest in T1DM females (31.4%) and lowest in T2DM males (6.9%) [23]. NHANES III study reported a higher prevalence of thyroid disease in diabetic subjects as compared to nondiabetics [21]. As per Greek study, the prevalence of thyroid dysfunction among T2DM was reported to be 12.3% with higher proportions in females than males [26]. A Saudi study of thyroid dysfunction among T2DM reported the prevalence of 16%, but the sample size was very limited [27]. A study from Jordan reported that thyroid dysfunction was present in 12.5% T2DM patients [28].

A recent population-based prospective cohort study conducted by Chaker *et al*. on 8452 participants to access thyroid function, who were free of diabetes at baseline reported that associated risk of developing diabetes was 1.09 times higher for every doubling of TSH levels mIU/L. Within the normal range, the risk of diabetes was 1.16 times higher with higher TSH levels. In participants with prediabetes, the associated risk of developing diabetes was 1.13 times higher for every doubling of TSH levels. Considerably, T2DM patients were more prone to thyroid disorders [1].

The prevalence of subclinical hypothyroidism (SCH) was reported to be about 4 to 8.5%, and can reach up to 20% in elderly women (over 60 years of age). In general population, the prevalence of SCH was reported to be approximately 2% [31] and in T2DM population about 10.2% [29-31]. As per NHANES III study, the prevalence of SCH in white, non-Hispanic women was reported to be 5.8% and 3.4% in men; while among blacks, non-Hispanic women 1.2% and 1.8% in men; further more in Mexican-American women and men it was 5.3% and 2.4% respectively [21]. Han *et al.* observed that the T2DM was associated with a 1.93 fold increase in risk of SCH. They observed that gender difference, old age, and an apparent geographic disparity were related to the prevalence of SCH in T2DM [31]. Among T2DM population, the women had 1.7 times higher prevalence of SCH than men and elderly T2DM (over 60 years of age) and were reported to experience SCH associated risks more frequently [31].

Thyroid hormone and Classification of Thyroid Disorders

Thyroglobulin and iodine are required for synthesis of monoiodotyrosine and diiodotyrosine, which are precursors for triiodothyronine (T3) and thyroxine (T4). The T4 is synthesized only in the thyroid, which

is inversely controlled by pituitary gland hormone TSH, while 80% of T3 can be produced by deiodination of T4 in specific tissues. The T3 have 10-times higher affinity than T4 on nuclear thyroid receptor proteins and further these receptor proteins activate the transcription and translation of growth hormone (GH), thyrotropin-releasing hormone (TRH), malic enzyme, myosin, calcium channel and so on [32-33].

The functional behavior of the thyroid hormones are fundamental in majority of the thyroid diseases and clinical states; reflecting normal, excessive or defective levels of thyroid hormones. Altered hormone levels are the basis of classification. Thyroid function tests (TFTs) are used in diagnosing hypothyroidism or hyperthyroidism in symptomatic patients. However, the interpretation of TFTs needs to be put in perspective as TFTs may reflect on non-thyroid pathology, such as hypothalamic or pituitary disease [32-34].

Euthyroidism means normal production of thyroid hormone (TH) by the thyroid, normal circulating and intracellular level of TH. Euthyroidism have normal TSH and free T4 (FT4) or TBG [33-35].

Hyperthyroidism means clinical symptomatology due to excessive circulating and intracellular TH. If the TH are produced by the thyroid in excess due to thyroid gland hyper-function, it is known as hyperthyroidism. If the excess level of TH is due to excess secretion rather than production without thyroid gland hyper-function, the condition is called thyrotoxicosis. Patients with hyperthyroidism have low or undetectable TSH and increased levels of FT4 or decreased TBG [33-35].

The term subclinical hyperthyroidism (SCH) describes a condition with low TSH level and normal serum concentration of FT4 or TBG. SCH has the same causes as overt hyperthyroidism [33-35].

Hypothyroidism is almost always due to the lack of TH production and inadequate replacement therapy. Patients with primary hypothyroidism have increased TSH concentration (as a result of the body's attempt to produce more TH), and low serum concentration of FT4 or increased TBG [33-35].

Effect on Glucose Metabolism

Chaker *et al.* has recently reported that hypothyroidism is associated with an increased risk of diabetes. Further they also described that pre-diabetics with hypothyroidism are at greater risk for progression to diabetes than pre-diabetics with euthyroid or hyperthyroid state [1]. Gronich *et al*. and Thvilum *et al*. also reported increased risk of diabetes in hypothyroid individuals [36-37]. While the Danish study by Brandt *et al*. reported opposite results, that an increased risk of diabetes in hyperthyroid individuals [38]. However, there are several factors that could explain these differences, like variance in the mean age, possible iodine status of the studied population and misclassification as Brandt *et al*. have not included laboratory measurements of thyroid function [1].

The relationship between hypothyroidism and the risk of diabetes can be explained by alteration of many pathways.TH is a major regulator of metabolism and energy expenditure. TH is directly involved in the control of insulin secretion and influences plasma glucose levels, insulin sensitivity, and carbohydrate metabolism by interacting to the liver, white adipose tissue, skeletal muscle, and pancreas [4, 39-40]. TH has been observed to preserve beta-cell viability and proliferation as well [41-42].

Glucose metabolism is affected via several mechanisms in hypothyroidism. It is observed that there is a reduced rate of liver glucose production via gluconeogenesis and glycogenolysis in patients with hypothyroidism [42]. Leong *et al*. reported that repeated hypoglycemic episodes are the presenting signs for the development of hypothyroidism in T1DM and replacement with TH reduces these episodes [43]. The hypothyroidism down-regulates the plasma membrane glucose transporters and premature insulin degradation [44-45]. The hypothyroidism and SCH have been recognized as insulin resistant states [46-47]. Studies have shown that this is due to impaired insulin stimulated glucose utilization in peripheral tissues [46-47]. Treatment of hypothyroidism has been revealed to restore insulin sensitivity and the secretion of glucoregulatory hormones [6, 48]. The hyperthyroidism is associated with insulin resistance but this high and high-normal thyroid functions are protective to progression of diabetes as the hyperthyroidism causes increased insulin secretion [41, 49-51]. In vitro studies suggest that T3 and Thyroid Receptor alfa (TRα) promote proliferation of pancreatic islet cell. T3 also stimulates the islet transcription factor Mafa, which contributes to the transition of islets to glucose-responsive insulin-secreting cells, which further improves the insulin secretion in presence of higher free T3 in prediabetics [50-51]. Studies suggest that during hyperthyroidism the release of insulin precursors increases but they are inactive form and due to that insulin degradation rate increases and the half-life of insulin is reduced [52-53]. The above mentioned hypothesis was supported by Bech *et al*., as they observed the increased proinsulin levels in response to a meal in untreated Graves' disease [54]. Other studies reported that untreated hyperthyroidism were associated with a reduced C-peptide to proinsulin ratio and suggested an underlying defect in proinsulin processing [55]. It was also observed that hyperthyroidism and high-fat diet result

in significant impairment of islet function [56]. Fazacappa *et al*. suggested that physiological T3 concentration prevents islet deterioration and maintains islet structure, size, and consistency [57]. Hence, it can be deduced that if the T3 concentration is within normal range it helps to maintain the islet structure, proliferation, and secretion of active insulin, while augmented T3 level overwhelms the islet cells, which causes improper proliferation and secretion of inactive insulin.

Hyperthyroidism causes increased liver gluconeogenesis and peripheral insulin resistance and is associated with glucose intolerance [58-59]. The non-oxidative glucose disposal enhanced during hyperthyroidism results in an over-production of lactate that further promotes hepatic gluconeogenesis [60]. It has been observed that elevated T3 stimulates gluconeogenesis, as treatment of T3 on hepatocytes up-regulates the gene expression of gluconeogenesis enzyme phosphoenolpyruvate carboxykinase (PEPCK) via upregulation of TRβ and CCAAT enhancer binding protein [61-62]. These upregulations were resistant to insulin suppression of hepatic glucose production compared with euthyroid [62-63]. Augmented T4 increases the transport of alanine to liver and increases gluconeogenesis [64]. TH also induces the synthesis of hepatocyte glucose transporter-2 (GLUT-2), which consequently increases hepatic glucose output and causes abnormal glucose metabolism [65-66].

The hepatic insulin resistance is mediated by sympathetic stimulation. The administration of T3 to the hypothalamic paraventricular nucleus increases glucose production via sympathetic input to the liver through interaction with the sympathetic nervous system, showing that the T3 effect was central [67]. Further, hyperthyroidism associated with release of growth hormone, glucagon, and catecholamine, which also contributes to the impaired glucose tolerance [68-69]. Another mechanism explaining the relationship between hyperthyroidism and hyperglycemia is increase in intestinal glucose absorption mediated by the excess TH [70-71].

Lipid Metabolism

TH affect lipoprotein metabolism. It has been observed that even in euthyroid state, the increased TSH level within the normal range causes an increase in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs) and a decrease in high-density lipoprotein cholesterol (HDL-C) [72-73].

TH up-regulates the cholesterol synthesizing 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase and LDL receptor gene expression through sterol regulatory element-binding protein-2 (SREBP-2) and via direct binding of T3 to specific thyroid response elements (TREs) [74]. TH can also affect the HDL-C metabolism by increasing cholesteryl ester transfer protein (CETP) activity, which exchanges cholesteryl esters from HDL2 to very low density lipoproteins (VLDL) and TGs from VLDL to HDL2 [75]. TH stimulates the lipoprotein lipase (LPL) via reducing the expression of angioprotein-like 3 (ANGPTL3), a potent LPL inhibitor. Over expression of ANGPTL3 significantly enhances TC, non-esterified fatty acid and TGs [76], while TH treatment reduced ANGPTL3 mRNA expression through TRβ and improves the condition [77-78].

TH up-regulates the gene expression of APOA5 (apolipoprotein A-V) and further the ApoA5 protein, which have been associated with decreased levels of TGs [78-79]. Patients with mutation of APOA5 manifest markedly reduced plasma LPL activity and hypertriglyceridemia [80]. Moreover, ApoA5 causes a greater clearance of lipoprotein remnants by increased hepatic uptake due to enhanced LDL receptor activity [78-79].

In hypothyroidism, the decreased thyroid function is accompanied by reduced activity of HMG-CoA reductase and increased serum TC, LDL-C, remnants of VLDL, Chylomicron (CM), oxi-LDL, ApoB [81-82], while TG, HDL-C, and VLDL are normal or slightly increased [83-85]. In hypothyroidism, TH decreases the LDL receptor expression and cholesterol absorption overshadow the effects of decreased hepatic cholesterol biosynthesis, leading to high serum levels of LDL-C, IDL-C, and TC levels [86].

Patients with hypothyroidism usually have higher LDL-C, leading to increased oxidized (oxi)-LDL. Oxi-LDLs are taken up by macrophages in the arterial walls to produce foam cells, and become a risk factor for atherosclerosis. The high levels of oxi-LDL are reversible with levothyroxine (L-T4) treatment [87]. Moreover, a decrease in LPL activity due to over expression of LPL inhibitor ANGPTL3 had been observed in hypothyroidism, which decreases the clearance of TG-rich lipoproteins and presented with elevated levels of VLDL and occasionally fasting chylomicronemia [88-89]. Hypothyroid patients were also observed to exhibit elevated levels of HDL-C, especially HDL2 due to reduced hepatic lipase (HL) activity which reduces the HDL2 catabolism to HDL3 [84, 90]. Hypothyroidism also inhibits the transcription of the apolipoprotein A1 (APOA1) gene, but the decreased activity of HL results in slower clearance of Apo A-1 protein, thus leading to increased Apo-A1 levels. Human studies show that Apo A-1 levels are decreased in hyperthyroidism and increased in hypothyroidism, whereas Apo A-2 levels are not influenced by either hyperthyroidism or

hypothyroidism [90-91]. Further, decreased activity of the CETP results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL-C levels [92]. Studies showed that lipoprotein (a) [Lp(a)] levels are increased in patients with hypothyroidism and decrease after levothyroxine (L-T4) treatment. The mechanism may be related to the decreased clearance of Lp(a) mediated by the LDL-R degradation pathway [23]. ApoB levels are higher in both overt and SCH and have been shown to decrease after L-T4 treatment [93-94]. The lipid abnormalities in overt hypothyroidism are reversible with L-T4 therapy unless the patient has underlying hyperlipidemia [95].

SCH is associated with increased levels of TC and LDL-C [96-99]. In addition, some studies have shown that SCH-induced dyslipidemia may also be accompanied by increased TGs [100-101] and decreased HDL-C levels [102]. Moreover, subjects with high normal TSH levels (2-4 mIU/L), but with positive TPOAb and TgAb may also exhibit elevated cholesterol levels [103]. Most studies have shown increased Lp(a) levels related to SCH [104-105]. An interesting study evaluated serum Lp(a) levels along with corresponding APOA phenotypes, which are known to influence Lp(a) levels, in SCH patients [106]. There is some controversy regarding the presence or the severity of SCH-induced dyslipidemia. Indeed, there have been studies indicating no significant difference in lipid profile between SCH patients and controls [89,107]. In hyperthyroidism, serum levels of total cholesterol, LDL-C and HDL-C are decreased and oxi-LDL levels are increased [108]. In hyperthyroid condition, TGs level showed either no change or decrease [90, 109], partly, due to T3 down regulation of ANGPTL3 and stimulates PLP, leading to hydrolysis of TGs. Then, T3-mediated LDLR stimulation dramatically increases clearing capacity for LDL-C [76]. The reason for the mild hyper-triglyceridemia is unclear. Lipolysis is augmented in hyperthyroidism with elevation of free fatty acids (FFA) in plasma, but hepatic lipogenesis is also augmented due to increased FFA flux from adipose tissue to the liver [82]. This increased lipolysis 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 TH [110].

Conclusion

Thyroid dysfunction and diabetes are closely associated with each other and characterized by a complex interaction. Insulin resistance states may increase thyroid gland nodularity. Uncontrolled hyperthyroidism in diabetes may trigger hyperglycemic emergencies while recurrent hypoglycemic episodes may exist in diabetic patients with hypothyroidism thus complicating diabetes management. Low and low-normal thyroid function also related to an increased risk of diabetes.In individuals with prediabetes and low and low-normal thyroid function, the risk of progression to diabetes more prominent. SCH is more prevalent in T2DM patients and that SCH may confer greater risk of diabetic complications. Furthermore, thyroid hormones also alter carbohydrate and lipid metabolism. Biochemical screening for thyroid dysfunction is critical in all dyslipidemic patients, as well as all patients with unexpected improvement or worsening of their lipid profile. Subsequent studies could address possible screening and treatment modalities for both diabetes and thyroid dysfunction. It is therefore important to diagnose thyroid dysfunction in diabetic patients and this practice should be inculcated in diabetic care. So, it's important for clinicians to identify the diabetic patients who are at risk for developing thyroid disorder and control the thyroid anomalies to reduce the chances of further complications.

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