

**THYROID DYSFUNCTION IN TYPE 2 DIABETES MELLITUS****Wilma Delphine Silvia CR<sup>1</sup>, Gandham Rajeev<sup>2</sup>, Venkata Bharat Kumar Pinnelli<sup>3</sup>****Abstract**

Diabetes Mellitus and thyroid disorders are two main endocrine disorders interrelated to each other and encountered in clinical practice. Diabetes patients have a higher prevalence of thyroid disorders than the normal population. Thyroid disease is found in both types 1 and 2 diabetes. A variety of thyroid abnormalities may co-exist and interact with diabetes mellitus. Diabetes mellitus appears to influence thyroid function in atleast two sites, one at the level of hypothalamic control of thyroid stimulating hormone (TSH) release and the other at the conversion of thyroxine (T<sub>4</sub>) to 3,5,3'-triiodothyronine (T<sub>3</sub>) in the peripheral tissue. Alterations in thyroid hormones indicate the characteristics of low T<sub>3</sub> syndrome. Marked hyperglycemia decreases the activity and concentration of hepatic T<sub>4</sub> -5' deiodinase. The relationship between diabetes mellitus and thyroid disorders is characterized by a complex interdependent interaction. Furthermore, it seems that unidentified thyroid dysfunction could negatively impact diabetes and its complications. Therefore, management of thyroid dysfunction in patients with diabetes may prove beneficial.

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## 1. INTRODUCTION

Diabetes Mellitus and thyroid disorders are two main endocrine disorders interrelated to each other and encountered in clinical practice. Their correlation is poorly understood and associated with vascular complications and responsible for high mortality and morbidity <sup>[1]</sup>. The association between diabetes and thyroid dysfunction had been recognized since 1979 and emphasized the importance of screening of diabetic patients to identify thyroid diseases <sup>[2,3]</sup>. Since then a number of the studies have reported the prevalence of thyroid dysfunction among diabetes patients to be between 2.2 to 17% <sup>[4]</sup>. However, few studies have observed very high prevalence of thyroid dysfunction in diabetes i.e. 31 % and 46.5% respectively <sup>[5]</sup>.

Diabetes patients have a higher prevalence of thyroid disorders than the normal population. Thyroid disease is found in both types 1 and 2 diabetes. Autoimmune disease associated thyroid dysfunction is commonly seen in type 1 diabetes. Type 2 diabetes is a metabolic disorder caused by insulin resistance, occurs primarily within the muscles, liver, and fat tissue. Since thyroid hormone regulate carbohydrate, lipid, and protein metabolism, with insulin and thyroid hormones being intimately involved in

cellular metabolism and thus excess or deficit of either of these hormones could result in the functional derangement of the other <sup>[6]</sup>. The term 'thyroid diabetes' was coined in the early literature to depict the influence of thyroid hormone alterations in the deterioration of glucose control <sup>[7]</sup>.

A variety of thyroid abnormalities may co-exist and interact with diabetes mellitus. The reported frequency of hyperthyroidism and hypothyroidism in patients with diabetes has varied from 3.2 % to 4.6 % and 0.7 % to 4.0 % respectively. Diabetes mellitus appears to influence thyroid function in at least two sites, one at the level of hypothalamic control of thyroid stimulating hormone (TSH) release and the other at the conversion of thyroxine (T4) to 3,5,3'-triiodothyronine (T3) in the peripheral tissue. Alterations in thyroid hormones indicate the characteristics of low T3 syndrome. Marked hyperglycemia decreases the activity and concentration of hepatic T4 - 5' deiodinase. The characteristic findings include low serum concentrations of T3, elevated levels of reverse T3 (rT3) and low, normal, or high levels of T4. The values return to normal after correction of hyperglycemia <sup>[8]</sup>.

## **Thyroid regulation of glucose Homeostasis:**

Common pathological mechanisms between diabetes and thyroid dysfunction has to be acknowledged that thyroid hormones exert profound effects in the regulation of glucose homeostasis. These effects include modifications of the circulating levels of insulin and counter regulatory hormones, intestinal absorption, hepatic production and the peripheral tissues uptake (fat and muscle) of glucose <sup>[8]</sup>.

While thyroid hormones stimulate hepatic gluconeogenesis, they also stimulate insulin-mediated glucose disposal in skeletal muscle and adipose tissue. Stimulation of hepatic glucose production by thyroid hormones may be a direct effect on liver gene transcription or an indirect effect, acting via a sympathetic pathway from the hypothalamus. Central interactions of thyroid hormones on glucose and lipid regulation also include 5' adenosine monophosphate-activated protein kinase (AMPK), the master-switch of energy homeostasis, as a central target. The modulation of insulin sensitivity as well as the feedback of thyroid hormones on appetite and energy expenditure have recently been extensively reviewed <sup>[8,9]</sup>.

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.

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. Activation of MC4R reduces food intake and increases energy expenditure and inactivating mutations in MC4R are associated with obesity. The repressive effect of T3 on the expression of MC4R helps in conserving energy in hyperthyroid states. 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 <sup>[9]</sup>.

### Effects of thyroid hormones at hepatic tissue:

Several genes involved in gluconeogenesis, glycogen metabolism and insulin signaling that are regulated by thyroid hormones in the liver have been identified. Importantly, pyruvate carboxylase the gluconeogenic enzyme involved in the formation of oxaloacetate through carboxylation of pyruvate in the mitochondria and phosphoenolpyruvate carboxykinase (PEPCK), the enzyme that catalyzes the rate-controlling step of gluconeogenesis by decarboxylation and phosphorylation of oxaloacetate to produce phosphoenolpyruvate, are a target of T<sub>3</sub>. Moreover, an increase in glucose-6-phosphatase mRNA expression, the enzyme that hydrolyzes glucose-6-phosphate and completes the final step in gluconeogenesis and glycogenolysis, with T<sub>3</sub> has been described [8,10].

A thyroid hormone mediated decrease in Akt2 (protein kinase B) mRNA expression, a serine/threonine kinase that is key in the insulin signaling pathway has also been reported. Akt2 participates in liver glycogen synthesis by inactivating glycogen synthase kinase 3, in charge of inactivating glycogen synthase. Thus, a decrease in Akt2 activity would in turn, decrease glycogen

synthesis explaining the antagonistic insulin effect of thyroid hormones at the liver. An induction of  $\beta$ 2-adrenergic receptor mRNA and repression of inhibitory G protein (Gi) RNA of the adenylate cyclase cascade by thyroid hormones were also reported. By this mechanism, thyroid hormones would facilitate the glycogenolytic and gluconeogenic effects of epinephrine and glucagon. An increased hepatic expression of the glucose transporter GLUT2 the principal transporter for transfer of glucose between liver and blood is also part of the insulin antagonistic effects of thyroid hormones at the liver that lead to an increased glucose hepatic output [11]. Most recently, a neural (autonomic) modulation of hepatic glucose metabolism by T<sub>3</sub> at the hypothalamus that takes place independently of plasma glucoregulatory hormone concentrations has been described. It was shown that upon selective administration to the paraventricular nucleus (PVN), T<sub>3</sub> increases endogenous glucose production and plasma glucose, and these hypothalamic T<sub>3</sub> effects are mediated via sympathetic projections to the liver. This response is independent of plasma T<sub>3</sub>, insulin, and corticosterone concentrations.

**Effects of thyroid hormones at the peripheral tissue:**

At peripheral tissues, thyroid hormones also regulate the expression of genes that affect glucose transport and glycolysis respectively. However, contrary to what happens at the liver level, some of these effects are synergistic with insulin. In skeletal muscle, the main site of insulin-mediated glucose disposal, glucose transporter GLUT4 is induced by thyroid hormone, revealing that T3 can increase basal and insulin-stimulated glucose transport in this tissue. It has also been reported that in skin fibroblasts the mRNA of the transcription Hypoxia-inducible factor 1 (HIF-1), a key mediator of glycolysis, increases in response to T3. Another target of thyroid hormones is peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 alpha), an essential transcriptional regulator of mitochondrial content and function, fatty acid oxidation, and gluconeogenesis. A decreased expression of PGC-1 alpha in the presence of diminished thyroid hormones can determine cellular lipid excess and impaired oxidative metabolism, characteristic of type 2 diabetes.

Apart from the serum levels of T3, the hormonal message is modulated by its intracellular concentration, dependent upon the activity of deiodinases. A lower

expression and activity of type 2 iodothyronine-deiodinase (D2), has been found to be associated with insulin resistance [8,12].

**Effect of Diabetes on Thyroid Function:**

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. Reduced T3 levels have been observed in uncontrolled diabetic patients. This “low T3 state” could be explained by impairment in peripheral conversion of T4 to T3 that normalizes with improvement in glycemic control. 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.

**Type2 Diabetes & Hypothyroidism:**

The diabetics showed trend towards hypothyroidism. The pathophysiology of thyroid dysfunction in diabetes is still unclear; however thyroid antibodies have been suggested to be the causative factors. Hypothyroidism & subclinical hypothyroidism are frequent co-morbidities in patients with DM, a TSH level determined at diagnosis of diabetes may predict hypothyroidism even at concentrations within

the reference range <sup>[13]</sup>. Hypothyroidism is characterized by impaired glucose absorption from gastrointestinal tract and delayed peripheral glucose assimilation and gluconeogenesis, decreased or normal hepatic glucose output and decreased peripheral tissue glucose disposal. Moreover, while in hypothyroidism the inability of insulin to sufficiently sustain glucose utilization by the muscles leads to insulin resistance. Subclinical hypothyroidism may also constitute an insulin resistance state. Glucose disposal is decreased in hypothyroidism, while glucose-stimulated insulin secretion is increased, presumably because of insulin resistance <sup>[13]</sup>. Patients with subclinical hypothyroidism sustain an obvious increase in cardiovascular event rates. Despite this, there is a distinct lack of relevant research into risk factors associated with microvascular complications in type 2 diabetes with subclinical hypothyroidism. Several studies focused predominantly on the issue of diabetic nephropathy, as defined solely by elevated microalbuminuria, rather than retinopathy. However, in most diabetic patients with elevated microalbuminuria, other chronic kidney diseases should be considered in the absence of diabetic retinopathy <sup>[14]</sup>.

### **Type2 Diabetes & Hyperthyroidism:**

Thyroid hormones affect glucose metabolism via several mechanisms. Hyperthyroidism has long been recognized to promote hyperglycemia. 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. Hyperthyroidism was associated with a reduced C-peptide to proinsulin ratio suggesting an underlying defect in proinsulin processing. Another mechanism explaining the relationship between hyperthyroidism and hyperglycemia is the increase in glucose gut absorption mediated by the excess thyroid hormones. 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. Additionally, increased lipolysis is observed in hyperthyroidism resulting in an increase in free fatty acids that stimulates hepatic gluconeogenesis. The increased release of

free fatty acids could partially be explained by an enhanced catecholamine-stimulated lipolysis induced by the excess thyroid hormones. 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 growth hormone, glucagon and catecholamine levels associated with hyperthyroidism further contributes to the impaired glucose tolerance. 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<sup>[8,15,16]</sup>.

### **Pathological mechanisms common to thyroid disorders and diabetes**

Thyroid hormones act differentially in liver, skeletal muscle and adipose tissue – the main targets of insulin action. Thyroid disorders have a major impact on glucose control. When thyroid dysfunction ensues the glucose homeostatic balance is broken. Insulin resistance, mainly associated with increased hepatic gluconeogenesis, is characteristic of an excess of thyroid hormones and explains why glucose control deteriorates when diabetic patients develop hyperthyroidism. Thyrotoxic patients show

an increased glucose turnover with increased glucose absorption through the gastrointestinal tract, postabsorptive hyperglycaemia and elevated hepatic glucose output, along with elevated fasting or postprandial insulin and proinsulin levels, elevated free fatty acid concentrations and elevated peripheral glucose transport and utilization. In peripheral tissues there is a massive arrival of glucose to the cells that overwhelms the Krebs cycle resulting in an increased metabolism of glucose through the nonoxidative pathway. Lactate produced in great quantities in the cells returns to the liver and participates in the Cori cycle where four ATP molecules are wasted for each glucose molecule that is created. Although glucose uptake in peripheral tissues has been described as either normal or increased reduced insulin stimulated peripheral glucose utilization has also been demonstrated in hyperthyroidism<sup>[17]</sup>.

### **CONCLUSION:**

The relationship between diabetes mellitus and thyroid disorders is characterized by a complex interdependent interaction. Furthermore, it seems that unidentified thyroid dysfunction could negatively impact diabetes and its complications. A higher frequency of cardiovascular events, retinopathy and nephropathy

was observed in diabetic patients with subclinical hypothyroidism. Therefore, management of thyroid dysfunction in patients with diabetes may prove beneficial.

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