

Review

DIABETES AND THYROID DISEASES - A REVIEW

R Sathish, V Mohan

ABSTRACT

The fact that insulin and thyroid hormones influence each other actions assumes significance since diabetes mellitus and thyroid disease are the two common endocrine disorders in adult population. Poorly controlled diabetes results in a low T3 state and a loss of TSH response to TRH. Regardless of glycemic control there is an absence of nocturnal TSH peak. There is an increased incidence of dysthyroid optic neuropathy in patients with Graves disease and co-existent diabetes. Also, the visual prognosis after treatment is poor. 50% of thyrotoxic patients who were previously euglycemic exhibit variable glucose intolerance while frank diabetes occurs in 2-3% cases. In diabetic patients presence of thyrotoxicosis deteriorates the glycemic control.

Diabetic patients with hypothyroidism may suffer from recurrent episodes of hypoglycemia. Type 1 diabetes mellitus patients have a high prevalence of thyroid dysfunction with nearly one third of all newly detected patients showing thyroid autoimmunity. Also, Type 1 diabetes mellitus and hypothyroidism co-exist in down's syndrome as well as congenital rubella. In autoimmune polyglandular syndrome Type 2, autoimmune thyroid disease and immune mediated diabetes are among the components.

KEY WORDS: Diabetes and thyroid function, Graves orbitopathy, Hyperthyroidism, Hypothyroidism, Autoimmune thyroid disease and type 1 diabetes.

INTRODUCTION

Diabetes mellitus and thyroid diseases are the two common endocrinopathies seen in the adult population. 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. This article will review how diabetes affects thyroid function in euthyroid individuals, how it affects pre-existing thyroid disorders, conversely how thyroid diseases

could affect the glycemic status and finally discuss clinical situations where both the diseases could co-exist.

EFFECT OF DIABETES ON THYROID FUNCTION

In euthyroid individuals with diabetes mellitus, the serum T3 levels, basal TSH levels and TSH response to thyrotropin releasing hormone (TRH) may all be strongly influenced by the glycemic status (1). Poorly controlled diabetes, both Type 1 and Type 2, may induce a "Low T3 state" characterized by low serum total and free T3 levels, increase in reverse T3 (rT3) but near normal serum T4 and TSH concentrations (2). Low serum T3 is due to reduced peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) via 5' monodeiodination reaction. Studies indicate that it may be the long term diabetic control that determines the plasma T3 levels (1). Poorly controlled diabetes may also result in impaired TSH response to TRH or loss of normal nocturnal TSH peak. TSH responses and "low T3 state" may normalize with improvement in glycemic status but even with good diabetes control, the normal nocturnal TSH peak may not be restored in C-peptide negative patients i.e. those with totally absent pancreatic beta cell function (3).

EFFECT OF DIABETES MELLITUS ON THYROID DISEASES (GRAVES ORBITOPATHY)

Dysthyroid optic neuropathy (DON) resulting in blindness is the most threatening complication of Graves' orbitopathy (GO). It is caused due to the compression of optic nerve by enlarged extraocular muscles at the orbital apex. Incidence of DON in patients with diabetes mellitus is higher than that seen in control "GO" group with some studies showing 10 fold rise in prevalence in diabetic patients. The higher prevalence has been explained by reduced oxygenation of optic nerve in diabetic patient owing to the vasculopathy making it more susceptible to the pressure

effect. Also it has been documented that the visual recovery after treatment in patients with DM and DON may not be as good as in non-diabetic patients (4).

EFFECT OF HYPERTHYROIDISM ON GLYCEMIC STATUS

Graves disease is the commonest cause of hyperthyroidism. While Graves disease may be associated with type 1 diabetes in polyglandular autoimmune syndrome, thyrotoxicosis by itself is diabetogenic. Variable glucose intolerance is seen in up to 50% of patients with graves and frank diabetes occurs in 2-3%, when hyperthyroidism develops in normal individuals. In known diabetic patients, the diabetic control deteriorates (2). Varied metabolic changes may occur as a result of hyperthyroidism and contribute to the deterioration of glycemic control status and these changes are outlined below.

1. Gastrointestinal System

In hyperthyroidism, there is accelerated gastric emptying, enhanced intestinal glucose absorption and an increase in portal venous blood flow (4).

2. Insulin Secretion

While some studies show decreased insulin secretion in hyperthyroidism (5, 6) most of the studies report either normal or increased levels of insulin in the peripheral and portal circulation (7). It is possible that there could be a masking of increase in insulin secretion due to increased degradation of insulin. In hyperthyroidism, the insulin clearance rate is reported to be increased by about 40% (8). Long term thyrotoxicosis has been shown to cause beta cell dysfunction resulting in reduced pancreatic insulin content, poor insulin response to glucose and decreased rate of insulin secretion (9).

3. Endogenous Glucose Production

In hyperthyroidism the endogenous glucose production is greatly increased by a variety of mechanisms: (a) there is an increase in the availability of gluconeogenic precursors in the form of lactate, glutamine and alanine from skeletal muscles and glycerol from adipose tissue, (b) there is an increase in the concentration of plasma FFA stimulating hepatic gluconeogenesis (10); (c) there is an increase in glycogenolysis due to inhibition of glycogen synthesis resulting in hepatic glucose output even in fed state (11); (d) there is an upregulation of

GLUT-2 glucose transporters protein expression in the hepatocyte plasma membrane. This permits increased glucose efflux to occur without intracellular glucose accumulation which would limit hepatic glucose production (12); (e) finally, there is increased secretion and exaggerated effects of glucagon and adrenaline on liver cells (10).

4. Glucose Utilization

Adipose Tissue

In adipocytes isolated from rats or hyperthyroid patients, the sensitivity of glucose transport and utilization to insulin has been found to be normal, increased or decreased. The varied results probably reflect to regional differences in the metabolic characteristics of isolated adipocytes (5.10).

Skeletal Muscle

In skeletal muscle, there is a preferential increase in glucose uptake and lactate formation relative to glucose oxidation and storage in hyperthyroid state. This is due to increase in both basal and insulin stimulated GLUT1 and GLUT-4 transporters (13), increased responsiveness of glycogenolysis to beta adrenergic stimulation (10), increased activity of hexokinase and 5 phosphofructokinase and decreased sensitivity of glycogen synthesis to insulin (14).

Thus the net effect of changes occurring at various levels such as gastrointestinal tract, beta cells, hepatocytes, adipocytes and skeletal muscles is hyperglycemia.

EFFECT OF HYPOTHYROIDISM ON GLYCEMIC STATUS

In hypothyroidism, the synthesis and release of insulin is decreased (6). The rate of hepatic glucose output is decreased probably due to reduced gluconeogenesis. A post receptor defect has been proposed to explain the decrease in insulin stimulated glucose utilization in peripheral tissues (10). The net effect is an increased risk of recurrent hypoglycemia in a diabetic individual (15).

INTERPLAY OF OTHER HORMONES

In addition to the impact of altered thyroid status per se on diabetes, hyperthyroidism is associated with an increase and hypothyroidism with a decrease in the

secretion of growth hormone and glucocorticoids further affecting glucose homeostasis (16, 10).

ASSOCIATION BETWEEN IMMUNE MEDIATED (TYPE 1) DIABETES MELLITUS AND AUTOIMMUNE THYROID DISEASES

Nearly one third of all newly detected Type 1 diabetes mellitus patients have co-existent thyroid autoimmunity (TAI) and a high prevalence of thyroid dysfunction which is predominantly hypothyroidism (clinical or subclinical) whilst a few have hyperthyroidism. The high prevalence of thyroid dysfunction emphasizes the importance of routine screening for TAI in all newly detected Type 1 diabetes mellitus patients followed by annual TSH assay in case TAI is positive (17,18).

Type 1 diabetes may be seen in association with hypothyroidism in Down's syndrome and also in patients with congenital rubella (2). Insulin requiring diabetes in association with primary hypothyroidism is sometimes seen in cases of haemochromatosis (2).

Autoimmune polyglandular syndrome type 2 (APS 2) which is more common in women and occurs in early to middle adulthood is characterized by autosomal dominant inheritance and presence of autoimmune Addison's disease, autoimmune thyroid disease and immune mediated diabetes. Grave's disease and Hashimotos thyroiditis are also common in APS2 (18, 19).

CONCLUSIONS

There is inter-dependence between insulin and thyroid hormones for normal cellular metabolism so that diabetes mellitus and thyroid diseases can mutually influence the other disease process (Table 1). When diabetes occurs in euthyroid individuals, it results in altered thyroid function tests with no clinical dysfunction. In a patient with preexisting Graves Orbitopathy, the risk of visual loss is increased and chances of visual recovery is less if co-existing diabetes is present. When hyperthyroidism occurs in the setting of euglycemia, 2-3% of these individuals may become diabetic. Hyperthyroidism results in deterioration of diabetic control while hypothyroidism increases the susceptibility to hypoglycemia in diabetic patients thereby complicating the diabetic management in these individuals.

TABLE 1: DIABETES MELLITUS – THYROID DISEASE INTERACTION

Clinical Condition	Effect on Glycemia	Effect on Thyroid function /Disease
Diabetes mellitus (DM)- In euthyroid individuals	---	↓ Serum T3 ↑ rT ₃ ↓ TSH response to TRH Impaired nocturnal TSH peak
Diabetes Mellitus-In hyperthyroidism individuals	Poor glycemic control	↑ Incidence of dysthyroid optic neuropathy
Hyperthyroidism - In euglycemic individuals	Glucose intolerance in 50% cases	---
	Overt diabetes in 2-3%	
Hyperthyroidism- In diabetic individuals	Deterioration of diabetes control	---
Hypothyroidism- In diabetic individuals	Predisposition to recurrent hypoglycemia	---
In Autoimmune Type 1 individuals	---	↑ Prevalence of thyroid disease

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