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REVIEW ARTICLE

Thyroid and Diabetes Interface

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INTRODUCTION

Diabetes mellitus, characterised by hyperglycaemia, is a health problem affecting the population worldwide in general and of India in particular. Uncontrolled diabetes with its many adverse effects like cardiovascular diseases, kidney diseases and dyslipidemias increase morbidity and mortality.

The impact of this disease on the quality of life, morbidity and mortality, through the complications that affect the small and large vessels, has been emphasised by the findings of the national commission (USA) on diabetes and DCCT trial.

In pursuit of controlling hyperglycaemia, a lot of emphasis is given in treating hypertension, dyslipidaemias etc. but the often forgotten fact is the presence of a second endocrine disorder like thyroid dysfunction which may be the root cause of poor glycaemic control and progressive morbidity and mortality.

The association between these two disorders has long been recognized, although the prevalence of thyroid dysfunction in diabetic population varies widely between different studies. With insulin and thyroid hormone, being intimately involved in cellular metabolism, excess or deficit of one of these hormones results in functional derangement of the other.

As diabetes is the most common endocrine and metabolic disorder, there was always a curiosity to understand and learn the association of this with the dysfunction of another endocrine gland, the thyroid. The aim of this review is to establish the relationship between the diabetes and thyroid function. It also highlights the relationship with other parameters like age, sex, insulin sensitivity, lipid profile etc., with or without associated thyroid dysfunction.

DIABETES AND THYROID: GENERAL CONSIDERATION

Udiong et al. have studied thyroid function in diabetes mellitus in Clabber, Nigeria. In that study, it was found that among the 161 diabetic subjects, 26.6% had low levels of thyroid hormone while 19.9% had raised levels. All the non-diabetic subjects showed euthyroid status. The incidence of hyperthyroidism was lower in females (8%) than in males (11%), but the number of subjects in hypothyroid state was higher in females (16.8%) than in males (9.9%).[1]

Patricia Wuin her article has stated that diabetic patients have a higher prevalence of thyroid disorders compared with the normal population. Patients with one organ-specific autoimmune disease are at risk of developing other autoimmune disorders, and as thyroid disorders are more common in females, it is not surprising that up to 30% of female type 1 diabetes patient have thyroid disease. A number of reports have also indicated a higher than normal prevalence of thyroid disorders in type 2 diabetes patients, with hypothyroidism being the most common disorder.[2]

Perros et al. demonstrated an overall prevalence of 13.4% of thyroid diseases in diabetes with the highest prevalence in type 1 female diabetics (31.4%) and lowest prevalence in type 2 male diabetics (6.9%).[3]

Recently, a prevalence of 12.3% was reported among Greek diabetic patients.[4] Sixteen per cent of Saudi patients with type 2 diabetes were found to have thyroid dysfunction.[5] In Jordan, a study reported that thyroid dysfunction was present in 12.5% of type 2 diabetic patients.[6] 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.[7] 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.[8]

Thyrodiabetesin Relation to AGE

Diabetes mellitus and thyroid disorders both are common in elderly. Due to the improvement of diagnostic procedures and increase in life expectancy, thyroid dysfunction is being diagnosed in increased proportion in diabetic patients.

Flatau et al. have also observed similar findings. They have reported 38% with sub clinical hypothyroidism after the age of 60 years. The prevalence of hypothyroidism was 14% (9.7% in male patients and 18.2% in female patients) and that of diabetes mellitus was 11.5% (12.1% in males and 11.1% in females). In 74% of the diabetic patients the diagnosis was made after the age of 60 years. They have concluded that diabetes mellitus and primary hypothyroidism are common disorders in elderly subjects and have an atypical presentation.[9]

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. The latter further observed an increase in 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 non-diabetic patients.[10]

THYROID DYSFUNCTION AND SEX

In a study from India, by Unnikrishnan et al., the overall prevalence of hypothyroidism was 10.95%. A significantly higher ($P< 0.05$) proportion of female vs. male (15.86% vs. 5.02%) and older vs. younger (13.11% vs. 7.53%) were diagnosed with hypothyroidism. Additionally, 8.02% (n = 430) patients were diagnosed to have subclinical hypothyroidism (normal serum-free T4 and TSH>5.50 μIU/ml).[11]

The prevalence of hypothyroidism in the overall study population was 10.95% (n = 587, 95% CI, 10.11–11.78) of which 3.47% (n = 186) were previously undetected and 7.48% (n = 401) were self-reported cases. Among all the cities, Kolkata recorded the highest prevalence of hypothyroidism (21.67%), while others showed comparable rates ranging from 8.88% (Hyderabad) to 11.07% (Delhi). Subclinical hypothyroidism (SCH) was observed in 430 (8.02%, 95% CI: 7.29–8.74) participants. Frequency of SCH was highest (8.93%) in the age group of above 55 years and lowest in the age group of 18–35 years (6.91%), though no statistically significant association was found with age (P = 0.1534). A significantly higher number of females (8.73%) than males (7.17%, P = 0.0358) were detected to have SCH. A total of 1171 (21.85%, 95% CI, 20.74-22.95) subjects tested positive for anti-TPO antibody. Females showed a greater prevalence (26.04%) than males (16.81%), $P< 0.05$.[11]

Among the adult population in India, the prevalence of hypothyroidism has been recently studied. In this population-based study done in Cochin on 971 adult subjects, the prevalence of hypothyroidism was 3.9%.The prevalence of subclinical hypothyroidism was also high in this study, the value being 9.4%. In women, the prevalence was higher, at 11.4%, when compared with men, in whom the prevalence was 6.2%. The prevalence of subclinical hypothyroidism increased with age.[12]

The prevalence of thyroid dysfunction was high and was commoner in women than men (24.7% vs. 18.2%). Subclinical hypothyroidism (SCH) was the commonest abnormality encountered and affected 19.3% subjects (15.9% men, 21.4%

women). The prevalence of SCH in men and women with TPO Ab was 15.8% and 25.9%, respectively. Overt hypothyroidism was the second commonest abnormality and affected a total of 181 subjects (4.2%).[13]

THYRO DIABETES WITH INSULIN SENSITIVITY

Consensus opinion regarding status of insulin sensitivity in hypo or hyperthyroidism is not yet available. Results of investigations have shown increased, decreased, or normal insulin sensitivity. Increased adrenergic tone of hyperthyroidism may alter basal insulin secretion.

McCulloch et al. suggested that insulin-stimulated glucose metabolism and inhibition of ketogenesis are normal in hyperthyroidism.[14] But in diabetic, it is markedly altered in the presence of insulin deficiency. Blood glucose levels are unaffected by hypothyroidism as insulin sensitivity is unaltered; there may be a decrease in exogenous insulin requirements and typically the glucose level remains stable or improves. Once treatment is initiated, normalisation of thyroid may lead to higher blood glucose levels and loss of diabetes control.[15]

THYROID DYSFUNCTION AND DIABETES SYMPTOMS AND COMPLICATIONS

Hage et al. concluded in their article stating the association between thyroid and diabetes, their effect on each other, and in relation to complications of diabetes. As stated in this article, hyperthyroidism leads to hyperglycaemia by more than one mechanism and hypothyroidism leads to recurrent episodes of hypoglycaemia thus requiring less dose of insulin.[16]

Satish and Mohan concluded that there is inter-dependence between insulin and thyroid hormones for normal cellular metabolism. When diabetes occurs in euthyroid individuals, it results in altered thyroid function tests with no clinical dysfunction. In a patient with pre-existing Gravesorbitopathy, the risk of visual loss is increased and chances of visual recovery are less if co-existing diabetes is present. When hyperthyroidism occurs in the setting of euglycaemia, 2–3% of these individuals may become diabetic. Thus early detection and treatment are good for better control of symptoms in these patients.[17]

Type 2 diabetic patients with subclinical hypothyroidism are associated with an increased risk of nephropathy and cardiovascular events, but not retinopathy. The higher incidence of cardiovascular events may be mediated by nephropathy.[18]

Yang et al. demonstrated recently that diabetic patients with subclinical hypothyroidism have more severe retinopathy than euthyroid patients with diabetes.[19] Den Hollander et al. in his study stated that treatment of hypothyroidism in diabetes improves renal function.[20]

Subclinical hyperthyroidism in diabetic patients may stimulate cardiac function and increase the risk of the atrial fibrillation.[21,22]

THYROID, DIABETES, AND LIPID PROFILE

Diabetes has been shown to be associated with numerous thrombotic, atherosclerotic, and cardiovascular diseases. Cholesterol has been singled out as the cause of atherosclerosis. However, other lipids, such as triglycerides and phospholipids, also show similar correlations. Diabetic patients show increase in lipid profile derangements. Presence of thyroid dysfunction increases risk of dyslipidemia in a diabetic patient in a greater proportion.

Patients with subclinical hypothyroidism tend to have higher levels of serum total and LDL cholesterol, apolipoprotein B, and Lp(a), where as levels of triglycerides, HDL cholesterol, and apolipoprotein AI did not differ significantly compared to euthyroid controls.[23–26] Despite the increased activity of the HMG-CoA reductase, levels of total cholesterol, LDL cholesterol, apolipoprotein B, and Lp(a) tend to decrease in patients with clinical or subclinical hyperthyroidism due to increased bile excretion of cholesterol and mainly to increased LDL receptor gene expression resulting in enhanced LDL receptor-mediated catabolism of LDL particles. Furthermore, HDL cholesterol levels are also decreased in hyperthyroidism due to increased CETP-mediated transfer of cholesteryl esters from HDL to VLDL.

Triglyceride levels remain unchanged. Therapy of hyperthyroidism results in restoration of the above mentioned alterations of lipid metabolism.[27,28]

Mean serum total cholesterol in untreated hypothyroidism was significantly higher ($p<0.001$) than after treatment (222.60±78.25 mg/dl vs. 159.81±39.51 mg/dl). Mean LDL cholesterol and HDL cholesterol decreased significantly after treatment in hypothyroidism (LDL 141.15±63.31 mg/dl before vs. 97.92±31.76 mg/dl after therapy, $p<0.001$; HDL cholesterol 40.52±11.59 mg/dl before vs. 36.67±9.84 mg/dl after therapy; $p<0.003$). Mean level of serum triglycerides in hypothyroid subjects decreased from 208.37±124.70 mg/dl to 134.10±77.56 mg/dl after treatment and the difference was statistically significant.[29]

CONCLUSION

Thyroid dysfunction is common in diabetic patients. Subclinical hypothyroidism is more common than other conditions. Females are more commonly affected. Elderly patients have higher incidence. Patients with thyroid dysfunction have poor glycaemic control even with treatment. Severe forms of diabetic complications are noted with presence of co-exiting thyroid disorders. One must have strong suspicion of thyroid dysfunction in patients with uncontrolled glycaemia and patients must be evaluated for thyroid function in such cases. In presence of type 1 diabetes, chances of hypothyroidism are more because of common cause of autoimmunity. Obesity and dyslipidaemia arising from hypothyroidism adversely affect the process of insulin resistance in type 2 diabetes. Thyrotoxicosis can lead to worsening of detected or undetected diabetes or can precipitate stress hyperglycaemia. For the therapeutic aspect, anti-thyroid drugs lower blood sugar, but thyroxine replacement may increase the blood sugar. This should be kept in mind during add on therapy for one disease after another. We should regularly check for thyroid function for early detection of thyroid disorders, so that we can prevent development of or delay the progression of complications as well as able to control blood glucose strictly.

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"It is better to change an opinion than to persist in a wrong one."

— Socrates