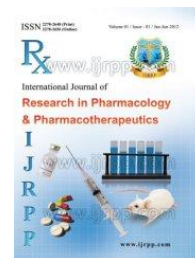




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Research article

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Review on rise of sister disease in type-II Diabetic patients

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ABSTRACT

Current review was regarding the thyroid gland disorder in those patients who are suffering with Type II Diabetes mellitus. Many studies were conducted regarding endocrine disorders. This review highlights the prevalence of thyroid disorder and its complications if it's not been treated at the correct stage. Current review details the underlying mechanism of thyroid dysfunction in people with type II diabetes mellitus and its reason. As thyroid dysfunction was asymptomatic in early stages, majority of the people neglects testing of thyroid biomarkers. As it increases it exposes in the form of clinical manifestations such as pigmentation, constipation, hives, weight gain/loss, loss of appetite, gray hair, unusual fatigue, tiredness increases. As it's a common fact that every individual knew thyroid was non-curable only maintenance was needed for lifelong. But when coming to the people with diabetes mellitus the condition was worsening, it leads to further complications and due to unknown reason in most of the patient's thyroid will be uncontrolled and in half of the patient's diabetes will lead to asymptomatic dysfunctioning of thyroid gland which is known as autoimmune disease.

Keywords: Biomarkers, Hypothyroidism, Hyperthyroidism, Diabetes mellitus, Prevalence.

INTRODUCTION

Among all endocrine metabolic diseases, Diabetes mellitus (DM) is a common metabolic disorder, which has been a leading cause of death worldwide, there was curiosity to understand and learn regarding its association with another endocrine disorders.¹⁻⁴ The term "THYROID DIABETES" was coined in early studies to depict the influence of thyroid hormone and its effect on glucose control.^{5,6} Diabetes mellitus and thyroid diseases are the two endocrinopathies seen commonly in the adult population. Insulin and thyroid hormones intimately involved in cellular metabolism and thus excess or deficit of either of these hormones could result in the functional derangement of the other.^{7,8} Diabetes mellitus as a

result of its common origin, the prevalence of hypothyroidism and hyperthyroidism was supposed to be similar to that of general population in patient with Type 2 DM. Hypothyroidism is one of the most common endocrine disorders, with a greater burden of disease in women and the elderly.¹ It is characterized that, hyperglycemia was resulting from a variable interaction of hereditary and environmental factors and is due to the combination of insulin resistance and defective secretion of insulin by pancreatic β -cells or both. Whereas thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism and excess or deficit of any one can result in functional derangement of the other.^{10, 11, 12} Thyroid disease is a pathological state

that adversely affects diabetic control and is commonly found in most forms of DM which is associated with advanced age in Type 2 diabetes and autoimmune diseases in Type 1 diabetes. DM appears to influence thyroid function in two sites; firstly at the level of hypothalamic control of TSH release and secondly at the conversion of T4 to T3 in the peripheral tissue. Marked hyperglycemia leads to reversible reduction of hepatic concentration of T4-5-deiodinase, low serum concentration of T3, elevated levels of reverse T3 and low, normal, or high level of T4. Since thyroid hormone regulates the body metabolic pathways and diabetes, it also alters the metabolism of food stuff which may be further affected due to the combination of thyroid disease and diabetes.¹³⁻¹⁶ Thyroid hormones directly control insulin secretion. In hypothyroidism, there is a reduction of glucose-induced insulin secretion by beta cells and the response of beta cells to glucose or catecholamine is increased in hyperthyroidism due to increased beta cell mass. Moreover, insulin clearance is increased in thyrotoxicosis.³ Glucose intolerance is associated with hyperthyroidism. Hypothyroidism is characterized by insulin resistance.¹ In Type 2 DM presence of highly frequent subclinical forms of hyperthyroidism and hypothyroidism should be ruled out since they may be associated with increased risk of nephropathy, retinopathy and cardiovascular events.²

EPIDEMIOLOGY

The WHO estimate of diabetes prevalence for all age groups worldwide was 2.8% in 2000 and 4.4% in 2030. The total no. of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. Overall 9.6% of persons aging over 20 and above are suffering with diabetes. Likely one person goes undiagnosed for every three persons currently diagnosed with the disease.¹⁸⁻²¹ Thyroid disorders are also very common in the general population and it is second to diabetes that affects the endocrine system. As a result it is common for an individual to be affected by both thyroid diseases and diabetes. The first report showing the association between diabetes and thyroid dysfunction were published in 1979.²³ A number of studies have estimated the prevalence of thyroid dysfunction among diabetes patients to be varying from 2.2 to 17%. However, fewer studies have estimated much higher prevalence of thyroid dysfunction in diabetes i.e.

31% and 46.5% respectively. This estimation has been increasing day by day, year by year.²¹⁻²⁴

ETIOLOGY

Sedentary lifestyle, dietary modifications, ethnicity, hypertension, habitual physical inactivity, impaired glucose tolerance, hereditary, smoking, alcoholism, delivering baby at lower weights, diseases (history of vascular diseases, polycystic ovarian disease, presence of acanthosis nigricans), drugs (diazoxide, glucocorticoids, nicotinic acid) and obesity have led to a dramatic increase in the incidence of diabetes mellitus, especially in the 21st century.²⁵⁻²⁸

PREVALENCE

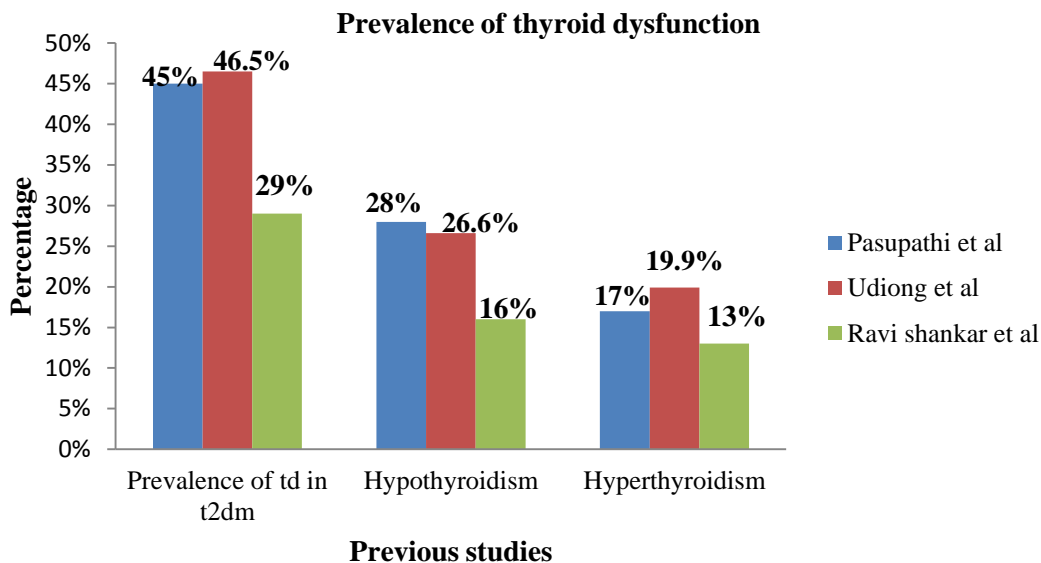
Prevalence of Diabetes mellitus in South-East Asia is 8.3% according to international Diabetes federation 75 million people have Diabetes. In other words, 1 in 12 adults suffering from Diabetes mellitus. Total Diabetes related deaths are estimated to be 1185 thousands in 2020.²⁹⁻³¹ The prevalence of subclinical hypothyroidism is higher in patients with metabolic syndrome which can be explained by concomitance of deranged serum lipid concentration, obesity, hypertension, insulin resistance in both these conditions.^{32, 33} It was observed that there was 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 non-diabetic. It's seen all over the world mainly in USA, UK, INDIA and many parts of world.³⁴⁻³⁶ Several reports documented a higher value than normal prevalence of thyroid dysfunction in the diabetic population. Particularly Perros 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 prevalence of 12.3% was reported among Greek diabetic patients⁷ and 16% of Saudi patients with Type 2 diabetes were found to have thyroid dysfunction. Symptoms are influenced by the severity of the hypothyroidism, as well as its rapidity of onset. Slow failure of thyroid function caused by autoimmune thyroiditis typically exists over years.⁸ Where the diagnosis is suspected, a neck examination should be performed looking for the presence or absence of a goitre or thyroid nodules, as well as a systematic examination considering both aetiology such as thyroidectomy scar, skin changes suggestive of

previous external neck irradiation, specific autoimmune diseases such as vitiligo, and signs of hypothyroidism. The spectrum of clinical presentations range from clinically unapparent disease to myxoedema coma, a rare endocrine emergency.⁹ Based on poor specificity of symptoms, hypothyroid patients may doesn't manifest clinical features that are suggestive to diagnosis without any abnormality of thyroid function. According to the survey conducted by many authors, thyroid dysfunction affected 6.6% of adults. Tunbridge reported prevalence of thyroid dysfunction in diabetes varied from 2.2 to 17% in these different areas.¹⁰ However, little is known regarding the thyroid size and structure in Type 2 diabetes mellitus given by Junik.⁶ Although several studies have shown the association between thyroid autoimmunity and Type 1 diabetes, Park and Menon reported that little is known regarding the risk of thyroid autoimmunity in subjects with Type 2 diabetes.^{7,8} Studies of Perros showed a prevalence of 13.4% and that of Papazafiropoulou 12.3%.^{9,10} A recent study in Tumkur, Karnataka showed the prevalence of hypothyroidism in Diabetes mellitus was 12.06%.¹³ Thyroid hormone act differentially in liver, skeletal muscle and adipose tissue the main targets of insulin action. While thyroid hormones oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis^{12,13} they upregulate the expression of genes such as GLUT-4 and phosphoglycerate kinase involved in glucose transport and glycolysis respectively, thus acting synergistically with insulin facilitating glucose disposal and peripheral utilisation.^{14,15} In hypothyroidism, glucose homeostasis is also affected although its clinical impact is less obvious. Decreased glucose disposal has been proved in hypothyroid patients by different methods including clamp study.^{16,17} Hypothyroidism results in unimpaired or decreased liver glucose output thereby compensating for insulin resistance present in peripheral tissues and accounting for the diminished insulin requirement for glycaemic control in hypothyroid diabetic patients.^{18,19,20} The association between these two disorders has long been recognized although the prevalence of thyroid dysfunction in diabetic population varies widely between studies. These both hormones being intimately involved in cellular metabolism and thus excess or deficit of these hormones result in functional derangement of the other. Enhanced sensitivity and specificity of TSH has greatly

impacts on the assessment of thyroid functions. Due to the improper control on diabetes and thyroid, it results in low T3 level and loss of TSH response to TRH. Regardless of glycemic control there is an absence of nocturnal TSH peak.^{21, 24} The aim of this study is to establish the relationship between the diabetes and thyroid dysfunction probably affected as a consequence to the autoimmune pathology. The thyroid dysfunction was assessed on the basis of clinical findings and laboratory estimation of serum T3 and T4 and TSH levels and structural disturbances were made out by FNAC of thyroid gland.^{23, 24} The present study was taken up to note the prevalence of thyroid dysfunction in Type 2 diabetics and spectrum of thyroid dysfunction. This article will review how diabetes affects thyroid function and conversely how thyroid diseases could affect the glycemic status.²⁶

EFFECT OF DIABETES ON THYROID FUNCTION

In thyroid 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. 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.²⁷ Low serum T3 is due to reduced peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) via 5 mono-deiodination reaction. Studies indicate that it may be the long term diabetic control that determines the plasma T3 levels.²⁸ 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 Many studies were conducted regarding the prevalence of thyroid and its functioning in diabetic patients and found the prevalence was gradually growing than older days with unknown reasons. This increase may be due to lack of symptoms or not keeping regular hormonal check-up. The values of thyroid dysfunction from various studies are as following (Graph-1)



Graph 1 Prevalence of Thyroid dysfunction: It indicates the prevalence of thyroid dysfunction and its compilation from various studies done over different parts of the world.

HYPOTHYROIDISM AND ITS IMPACT ON GLYCEMIC STATE

In hypothyroidism, the synthesis and release of insulin is decreased. 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.³²The net effect is increased risk of recurrent hypoglycemia in diabetic patients.³⁵⁻³⁷. Occasionally other endocrine disorders such as abnormal thyroid hormones levels are found in DM. The physiological and biochemical relationship between insulin and the iodothyronines on the metabolism of carbohydrates, proteins and lipid are studied. Such studies indicate that iodothyronines are insulin antagonist with high levels of diabetogenic, while absence of the hormone inhibits the development of diabetes.³⁸⁻⁴². DM and hyperthyroidism affect the levels of carbohydrates, proteins and lipids. Reports of the thyroid functions refers to follicular cell function, that includes measurement of hormones of the gland such as iodothyronine, carrier protein levels, thyroid stimulating hormone (TSH) and releasing hormone(TRH).⁴³⁻⁴⁶. The effects of iodothyronine on various metabolic pathways were recorded by

using specific tests such as TSH, FT4 and FT3. These tests reports and warrant further investigations into the relationship between diabetes mellitus and thyroid follicular cell function.³². The prevalence of diabetes with thyroid was seen high in female population when compared to male population it was proved by many studies conducted by Palma, Radaideh, Udiong, Umpierrez, Witting. The frequency of the cases are gradually increasing it may be due lack of knowledge, lack of symptoms, lack of evidence that diabetes will cause thyroid dysfunction.⁴⁶⁻⁴⁹

CONCLUSION

From threw this review we found that, the chance of thyroid dysfunction may be seen high in females when compared to males and chances of acquiring hypothyroidism was high than hyperthyroidism in regardless of age. Hereby this review shows the prevalence of abnormal thyroid hormone level among diabetic patients. The relationship between thyroid disorders and diabetes mellitus was found to be more complex. Failure to recognize the presence of abnormal thyroid hormone level in diabetes may be a primary cause of poor management often encountered in some treated diabetics. Therefore a routine assessment of thyroid hormone level in addition to other biochemical parameters in the early stages of diabetes will help in management of diabetes particularly in those patients whose conditions are difficult to manage.

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