



ASSOCIATION BETWEEN DIABETES AND THYROID DISORDERS

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Abstract

Diabetes mellitus and thyroid dysfunction are the two well-known endocrine disorders which are experienced in clinical practice. Different studies have evidenced that diabetes and thyroid disorders mutually influence each other and both disorders tend to co-exist. The unidentified thyroid disorders may adversely affect the metabolic control and increase the risk of secondary complications in diabetic patients. Insulin secretion and clearance is directly controlled by thyroid hormones. In hypothyroid condition, glucose-induced insulin secretion by β -cell is reduced. While in the hyperthyroid condition the resistance of insulin is increased. The prevalence of thyroid disorders is comparatively higher in diabetic patients than in general population. Diabetes and thyroid disorders mutually influence each other and both disorders tend to co-exist. The present study was conducted to evaluate thyroid status in type II diabetic patients and to understand the association between diabetes mellitus and thyroid disorders. The association between diabetes and thyroid disorders was significantly difference, interdependency of these two conditions and evaluation of thyroid hormones level along with the diabetic profile in the early stage of diabetes is recommended. This will help in the management of diabetes and can delay and avoid the progression of the secondary complications in diabetic patients with uncontrolled diabetes.

Keywords : Diabetes Mellitus, Thyroid Dysfunction, Hypothyroidism, Hyperthyroidism, patients.

Introduction

Worldwide thyroid diseases are the second well-known endocrine disorders after diabetes. In accordance with the recent report, 300 million individuals are suffering from thyroid disorders, of these, 42 million people live in India. Women are at higher risk of thyroid disorder than men. One out of eight women is at risk of suffering from thyroid disease during their lifetime (Prabhakar, 2016; Malik *et al.*, 2013, 2016). The exact reason for higher prevalence is still not clear, but it may be related to estrogen and progesterone (Nimmy *et al.*, 2012; Singh and Thakur, 2018; Singh *et al.*, 2019). Several commonly used medicines may cause interaction with thyroid gland function; such amiodarone which effects directly on the thyroid gland, while others drugs may affect indirectly, by affecting TSH levels such as glucocorticoids and dopamine. The binding of T4 to TBG is affected by heparin, and the conversion of T4 to T3 is affected by propranolol (Mitrou *et al.*, 2011; Dehaki *et al.*, 2017).

Prevalence of thyroid disorders

In general population, the prevalence of thyroid disorder has been reported to be 6.6%, and hypothyroidism being the most well-known thyroid disorder. Many investigations have demonstrated a comparatively higher prevalence of thyroid disorders in women (4 to 21%) than men (2.8 to 16%) (Kar *et al.*, 2018; Farooq 2019a, 2019b). Thyroid disorders increase with the advancing of age. Colorado study revealed that individuals with age of \geq 65 years had a prevalence rate of 18.5% which is higher than 18 years of age who had a prevalence rate of 3.5% (Johnson, 2006; Singh *et al.*, 2016; Sharma *et al.*, 2019). The result has shown 22.16% subjects were having thyroid dysfunction. Among them 4.24 % were overt hypothyroid, 9.44% were subclinical hypothyroid, 2.5% overt hyperthyroid and 5.97% were found to be subclinical hyperthyroid (Deokar, *et al.*, 2016). A study conducted by Wickham *et al* have shown the

prevalence of thyroid disorder to be 6.6% in the UK (Dehaki *et al.*, 2017).

(i) Hyperthyroidism: Those areas where sufficient iodine is available, approximately 1.3 percent of the general population have hyperthyroidism, comparatively more affecting women (2%) than men (0.2%). The severity of the disease can vary from subclinical hyperthyroidism to life threatening thyroid storm. In thyrotoxicosis condition, there is an excessive amount of thyroid hormones and high sensitivity to blood catecholamines which result in the clinical manifestations. The fundamental drivers of hyperthyroidism are:

- Graves' disease:** This is an autoimmune disease and main cause of hyperthyroidism (Prasher *et al.*, 2018). In this case, thyroid-stimulating autoantibodies stimulate thyroid gland growth and the production and release of thyroid hormones are increased.
- Toxic multinodular goiter:** Caused by diffuse follicular cell benign hyperplasia. The thyroid gland produces a large amount of thyroid hormone independent of the normal TSH regulation. People who are living in iodine-deficient areas and elder than 60 years are at higher risk (Prabhakar *et al.*, 2013, 2014, 2020; Sharma *et al.*, 2017).
- Toxic adenoma:** Accounts for approximately 5% cases. Caused by focal follicular cell benign hyperplasia that secretes excess thyroid hormone. This decrease TSH production which results in contralateral thyroid lobe suppression.

In addition use of some drug like amiodarone a class III antiarrhythmic agent and long-term use of lithium can cause hyperthyroidism (Mitrou *et al.*, 2011; Wu, 1999; Nankar *et al.*, 2017). The common symptoms of hyperthyroidisms are; heat intolerance, weight loss, irritable behavior, tremor, increase blood pressure, increase heartbeats, palpation, arterial fibrillation, warm dilated peripheries, infrequent

menstrual periods, sexual impotence and difficulty in speaking (Kaur *et al.*, 2016; Kaur *et al.*, 2020; Kumar *et al.*, 2019). Other gastrointestinal symptoms are constipation, diarrhea, and vomiting. Neurological symptoms such as mania, depression, incident dementia and the cognitive problem can be a manifestation of hyperthyroidism in the aged people. Hyperthyroidism may give rise to insulin resistance, which can cause glucose and lipid aberration through several processes such as; increase hepatic glucose production, increase the rate of lipolysis in adipose tissues, decrease the rate of insulin-stimulated glucose consumption in muscles and adipose tissues. Hyperthyroidism in grown-ups can also cause sleeplessness, hyperreflexia, nervousness, hyperactive, lack of focus and concentration (Johnson, 2006; Mitrou *et al.*, 2011; Amar *et al.*, 2016).

(ii) Overt and subclinical hyperthyroidism: It is defined as “decreased level of TSH in serum and increased level of thyroid hormones commonly cause by TSH receptor stimulation through autoantibodies (Graves’ disease) or autonomous production of thyroid hormones by thyroid nodules”. In general population, the prevalence of overt hyperthyroidism is 0.5 percent. Subclinical hyperthyroidism is characterized as serum TSH levels below the defined lower limit of the reference value (< 0.3 or 0.4 mU/l), with normal serum level of thyroid hormones. Exogenous and endogenous factors can lead to subclinical hyperthyroidism. Overtreatment with thyroid hormones is the most common cause of subclinical hyperthyroidism. Grave’s disease or autonomous functioning thyroid nodules may cause spontaneous subclinical hyperthyroidism. Subclinical hyperthyroidism may be related to insulin resistance. In general population, non-pregnant, adult population the prevalence of endogenous subclinical hyperthyroidism is 2% (Mitrou *et al.*, 2011; Gomberg-Maitland and Frishman, 1998).

(iii) Hypothyroidism: Hypothyroidism is the most well-known thyroid disease. Approximately 95% of thyroid disease is due to primary hypothyroidism and it is more common in women than men. In this case, the defect is mainly within the thyroid gland itself. Hypothyroidism occurs due to insufficient production of thyroid hormone or inefficient action of thyroid hormone on the target tissues. However, it may occur due to the defect anywhere along the hypothalamic-pituitary-thyroid axis, such as insufficiency of TRH, TSH or consumptive hypothyroidism due to inactivation of thyroid hormone (Chauhan *et al.*, 2017).

Being a hypometabolic condition it is specified by relative resistance to catecholamines. The main causes of hypothyroidism are:

- (a) **Iodine deficiency:** Globally, dietary iodine deficiency is the main reason for hypothyroidism.
- (b) **Chronic autoimmune thyroiditis (Hashimoto’s disease):** cell and antibody-mediated demolition of the thyroid gland.
- (c) **Iatrogenic causes:** This includes, external radiotherapy, radioiodine therapy, and thyroidectomy. Hyperthyroidism drug such as carbimazole, propylthiouracil and amiodarone, Iodine, lithium, and rifampicin can all cause hypothyroidism.
- (d) **Rarer causes:** It involves post-partum thyroiditis, post viral infection, or infiltrative diseases like amyloidosis and sarcoidosis (Mitrou *et al.*, 2011; Amar *et al.*, 2016).

The common symptoms of hypothyroidism are; cold intolerance, increase in weight, fatigue, dry skin, and hair, bradycardia, proximal myopathy, myotonia, peri-orbital edema, deafness, psychosis/dementia, and anemia. Hypothyroidism in mature individuals can cause dumbness, reduce reflexes, lethargy, slower cognitive function, more sleep and psychological disturbance. Hypothyroidism may cause insulin resistance which can lead to glucose and lipid aberration by several mechanisms such as decreased rates of insulin-stimulated glucose consumption in muscles and fat tissues, decrease the rate of triglyceride clearance leading to elevated levels of plasma triglycerides (Johnson, 2006; Mitrou *et al.*, 2011; Amar *et al.*, 2016).

(iv) Overt and subclinical hypothyroidism: Overt hypothyroidism is defined by elevated serum level of TSH (TSH > 10 mU/l) and low serum level of free T4 ($< 9-10$ pmol/l). The prevalence of overt hypothyroidism in general population, non-pregnant adults is 0.2-2.0 percent. Subclinical hypothyroidism is defined by elevated serum TSH level, with serum level of thyroid hormones within the normal range. It can be mild (TSH $> 4.0-4.5$ mU/l, but < 10.0 mU/l) or severe (TSH > 10.0 mU/l). The prevalence of subclinical hypothyroidism in the general adult population is 4-20 percent. Old people (whose age > 60 years) and women are more susceptible to be affected by subclinical hypothyroidism (Gomberg-Maitland and Frishman, 1998). Subclinical hypothyroidism is related to a group of cardiovascular risk factors such high blood pressure, dyslipidemia, hyperuricemia, diabetes mellitus and development of insulin resistance which approved by both in vivo and in vitro studies. Insulin resistance may result to decrease the insulin-stimulated rate of glucose transport in cells, through impaired translocation of GLUT4 glucose transporter on the plasma membrane (Mitrou *et al.*, 2011). A study conducted by Naomi Gronich *et al.* In Israel, has shown that hypothyroidism is a risk factor for diabetes mellitus. Subclinical hypothyroidism related risk for diabetes mellitus is prominent only upon statin use. Treating hypothyroidism and subclinical hypothyroidism might reduce the risk of diabetes mellitus (Gronich *et al.*, 2015).

Correlation of thyroid dysfunction with diabetes mellitus

There is a complex interdependent interaction between thyroid disorders and diabetes mellitus which are outlined below:

- Thyroid gland nodularity is increased by insulin resistance state.
- The risk of the visual loss may increase in Graves’ disease patient who has diabetes also.
- Hyperthyroidism causes poor glycemic control in diabetic patients.
- Hypothyroidism may complicate diabetes management by increasing susceptibility of the patient to hypoglycemia.
- Thyroid hormones interact with leptin, adiponectin, and gastrointestinal hormone such as ghrelin which may cause an alteration in carbohydrate metabolism (Ogbera and Kuku, 2011).

The correlation between T2DM and thyroid dysfunction is not fully understood, because of its complex mechanisms. It includes many variables such as:

- Synthesis of TRH
- Circadian rhythm of TSH

- Insulin resistance
- Autoimmunity
- Use of metformin, a commonly used drug for diabetes, and this drug has TSH lowering properties (Kalra, 2014; Subekti *et al.*, 2018).

Frequency of Co-occurrence

Several studies, conducted on many bases such as community, clinic, and indoor patient based have shown an increase in the prevalence of thyroid dysfunction in both Type 1 and Type 2 diabetes in all age groups. Studies conducted in India have shown that type 2 diabetic patients have 28-30% thyroid dysfunction, which occurs mostly in the form of clinical or subclinical hypothyroidism. The chances of co-occurrence of these two endocrine conditions are due to the autoimmune link between thyroid disease and T1DM, and high prevalence of thyroid dysfunction in obese people, and obesity is one of the risk factors for T2DM, In addition, the prevalence of both disorders is found to increase with the advancing of age which contribute to the association between the two diseases (Kadiyala *et al.*, 2010; Kalra, 2014).

Hyperthyroidism and diabetes

The incidence of hyperthyroidism is more in diabetic individuals as compared to the general population. A study conducted by Perros *et al* have shown 1% the occurrence of hyperthyroidism in diabetic patients which is comparatively higher than in the general population (about 0.3%) reported by Whickham survey (Kadiyala *et al.*, 2010). The most common reasons for hyperthyroidism in general population are Graves' disease and toxic nodular disease whereas the less common causes involve thyroiditis and drug-induced hyperthyroidism. Hyperthyroidism may cause various metabolic changes that contribute in worsening of glycemic control status (Sharma and Shivgotra, 2015) and these changes occur at different levels such as gastrointestinal tract, hepatocytes, beta cell, adipocytes and skeletal muscles which are outlined below:

- Gastrointestinal tract:** Hyperthyroidism speed up the gastric emptying. This increases the gastrointestinal absorption of glucose and enhanced in portal venous blood flow (Kalmann and Mourits, 1999).
- Secretion of insulin:** Most of the studies evidenced either normal or increased level of insulin in the portal and peripheral circulation. This may be due to:
 - Increased degradation of insulin
 - Increase in the clearance rate of insulin, which is reported about 40%.

Some other studies showed decrease secretion of insulin in hyperthyroidism. Prolonged thyrotoxicosis causes dysfunction of the beta cell resulting in decrease pancreatic insulin content, poor insulin response to glucose, and reduced rate of insulin secretion.

- Production of Endogenous glucose:** The production of Endogenous glucose is increased in hyperthyroidism through various mechanisms which outlined as follows:
 - More availability of gluconeogenic precursors such as lactate, alanine, and glutamine from skeletal muscles, glycerol from adipose tissues.
 - High concentration of plasma free fatty acids (FFA), which stimulate hepatic gluconeogenesis.

- Increase in glycogenolysis due to inhibition of glycogen synthesis, which results in hepatic glucose output even in the fed state.
- Upregulation of GLUT-2 glucose transporter protein expression in the hepatocyte plasma membrane. This allows glucose to come out and do not accumulate within the cell
- Increased secretion of glucagon and adrenalin and its high effects on the liver cells

4. Utilization of Glucose: In the hyperthyroid state, there is an increase in glucose uptake and lactate formation as compared to glucose oxidation and storage due to;

- Increase in the basal and insulin-stimulated GLUT1 and GLUT-4 transporters.
- Beta-adrenergic stimulation which increases glycogenolysis.
- Increase activity of hexokinase and phosphofructokinase.
- Decrease sensitivity of glycogen synthesis to insulin

In addition, the co-existence of diabetes and hyperthyroidism causes neurological complications, and increase the risk of fractures, which are the main reason for disability and morbidity, particularly in elderly patients (Singh *et al.*, 2014).

Hypothyroidism and diabetes

Hypothyroidism is one of the most well-known types of thyroid disorders in general population as well as in diabetes. Perros *et al* reported the occurrence of hypothyroidism 5.7% in diabetic patients while in accordance with Whickham survey the prevalence of hypothyroidism is 1.1% in general population The main cause of hypothyroidism in iodine sufficient territories is Hashimoto's disease (chronic autoimmune thyroiditis), other causes include, external radiotherapy, radioiodine therapy, thyroidectomy and hyperthyroidism drug such as carbimazole, propylthiouracil. Amiodarone, Iodine, lithium, and rifampicin can all cause hypothyroidism (Kadiyala *et al.*, 2010).

In hypothyroidism, the synthesis and secretion of insulin are decreased. Hepatic glucose output is reduced, which may be due to a decrease in the process of gluconeogenesis and peripheral glucose utilization. This can result in an increased risk of recurrent hypoglycemia and insulin resistance in diabetic patients, which complicate diabetes management (Nurakat *et al.*, 2019). Hypothyroidism can decrease the insulin requirement in diabetic patients as well as reduce the renal clearance of insulin. Hypothyroidism is more general in diabetic patients than Hyperthyroidism. Both Hypothyroidism and diabetes are linked by various common clinical features such as; overweight, obesity, hypertension, dyslipidemia, and depression. Coexistence of both these condition leads to higher risk of insulin resistance and make a person susceptible to cardiovascular disease (Kalra, 2014).

In hypothyroid patient diabetes may affect the efficacy of thyroid hormones treatment. In addition, the use of antidiabetic medication such as metformin interacts with thyroxine treatment and suppresses the TSH concentration in diabetic subjects (Kadiyala *et al.*, 2010; Chilakapati *et al.*, 2019). A retrospective study performed by Whitehead C *et*

al. In (2010) in Christchurch Hospital to find out the efficacy of annual screening for hypothyroidism requiring thyroxine treatment in the diabetes center. The result has shown 10.8% hypothyroidism in both T1DM 1 and T2DM and hypothyroidism requiring thyroxine treatment was 6.8% in T1DM diabetes and 6.0% in T2DM with greater prevalence in women than men. In T1DM patients after the age of 50 years hypothyroidism requiring thyroxine treatment increases, while in type 2 diabetes somewhat later (Whitehead *et al.*, 2010). Joffe BI *et al.* In 2014, in Johannesburg, South Africa conducted a study to evaluate the association of both T1DM and T2DM with hypothyroidism. The result showed that out 504 patients with known Type1 diabetes there were 102 patients (20.2%) and out of 918 Type 2 diabetic patients, 108 patients (11.8%) had hypothyroidism with significantly higher prevalence in women than men. The close relation between hypothyroidism and T1DM is due to the autoimmune predisposition and it is clinically proved that patients who have one organ-specific autoimmune disease are at high risk of progressing other autoimmune diseases (Joffe and Distiller, 2014). Another retrospective cross-sectional study conducted by Sanaa Al-Summary *et al.* (2015) at Sultan Qaboos University Hospital (SQUH) in Sultanate of Oman. 285 Omani diabetics' patients with known thyroid function were compared with a randomly selected healthy individual with known thyroid function as a control group. In diabetic patients, thyroid dysfunction was comparatively higher 12.6% than in the control group 4.9%. Among the female diabetics, the prevalence was higher (86%) as compared to male (14%). Hypothyroidism was the commonest (4.6%) thyroid dysfunction among the diabetics and subclinical hypothyroidism was observed in less controlled diabetics (Al-Sumry *et al.*, 2015).

Subclinical hypothyroidism and diabetes

Elevated TSH (thyroid stimulating hormone) level in serum in the presence of normal thyroid hormones is known as subclinical hypothyroidism. Recently conducted studies demonstrated that subclinical hypothyroid diabetic patients have more severe retinopathy and nephropathy as compared to euthyroid patients with diabetes. About one in 20 women suffering from T2DM is affected by Subclinical hypothyroidism (Kadiyala *et al.*, 2010).

Sriram Shanmugam *et al.* in 2015 conducted a prospective descriptive study on 186 diabetes patients who enrolled in the outpatient diabetic clinic of Sri Ramakrishna Hospital, Coimbatore, Tamil Nadu. In diabetic patients, the prevalence of thyroid dysfunction was 21.5 %. Subclinical hypothyroidism was the most common (12.4%) thyroid disorder, followed by subclinical hyperthyroidism (6.5%), then primary hyperthyroidism which was 2.7% and primary hypothyroidism (0%). In uncontrolled diabetes i.e. HbA1c ≥ 7 the prevalence of thyroid disorder is more common and high in the age group of < 50 years (Shanmugam *et al.*, 2015).

Effects of thyroid hormones on the regulation of blood glucose

Thyroid hormones are engaged in the mechanisms which regulate the function of pancreas and carbohydrate metabolism. Active thyroid hormone T3 (triiodothyronine), regulate a number of genes which are involved in carbohydrate metabolism, by exerting its action via binding to the receptors. These T3 receptors were derived from two

separate genes which encode the major T3 binding isoform, TR α 1, TR β 1, TR β 2, and TR β 3. Among these receptors, TR α 1 is predominantly concerned with the metabolic effects of the endocrine gland (Chidakel *et al.*, 2005; Arya *et al.*, 2013). Thyroid hormone can affect glucose homeostasis by its action on various organs systems such as liver, muscles, pancreas, and kidney. Excessive thyroid hormone results in altered glucose metabolism which can lead to diabetic ketoacidosis and thyroid storm. Thyroid hormone increases:

- Hepatic synthesis of glucose
- Increased gastrointestinal absorption of glucose
- Decrease peripheral glucose disposal
- Decrease storage of glycogen in the liver and skeletal muscles
- Change in oxidative and non-oxidative glucose metabolism
- Decrease the output of active insulin from the pancreas
- Enhances insulin resistance
- Increases the clearance of insulin through kidney

Thyroid hormones interact with adiponectin and gut hormones such as ghrelin. Adiponectin is secreted by adipose tissues. It has insulin-sensitizing characteristics, and low level of adiponectin increases the risk of T2DM (Duntas *et al.*, 2011; Sharma *et al.*, 2018).

Effects of thyroid hormones on Glycated Hemoglobin (HbA1c)

Glycated hemoglobin arises from the non-enzymatic addition of glucose at the N-terminal valine residue of the β -chain of hemoglobin, and the concentration of HbA1c indicates plasma glucose control over the past eight to twelve weeks. It is used to evaluate glycemic control in diabetic individual and may be helpful in the early detection of diabetes mellitus. In 2011 the WHO approved its use for the assessment of diabetes with a cut-Off value 6.5 percent. The ADA (American Diabetes Association) recently suggests HbA1c target value of lower than 7% for type 2 diabetes. Several studies approved the idea that lower levels of HbA1c are related to a decrease in microvascular and neuropathic complications.

Large retrospective meta-analysis has shown, elevation in HbA1c is related to a higher risk of cardiovascular diseases. Increase HbA1c concentration is related to cardiac disease and mortality regardless of a diagnosis of diabetes. The risk of the coronary heart disease related to glycemic control independent of whether the patient is diabetic or not (Ahmed *et al.*, 2017).

Kim MK *et al.* In 2010 conducted a study on 180 euthyroid subjects as control and 45 nondiabetic patients with overt hypothyroidism to find the effect of thyroid hormone on glycated hemoglobin HbA1c and glycated albumin (GA) in overt hypothyroid nondiabetic patients. The result revealed a higher level of HbA1c in hypothyroid patients as compared to the control subjects. The thyroid hormone replacement cause decrease in the HbA1c level and increase in the serum erythropoietin, mean corpuscular hemoglobin (MHC) and immature RBC count. Similarly, serum glycated albumin level is decreased by thyroid hormone replacement (Kim *et al.*, 2010).

Impact of Thyroid Hormones on Insulin Secretion and Sensitivity

Insulin secretion is instantly controlled by thyroid hormones. High level of thyroid hormones causes increased in the mass of beta cells, as a result, the response of the β -cell to glucose and catecholamine is increased and insulin clearance is enhanced. Low level of thyroid hormones causes a decrease in glucose-induced insulin release by β -cells.

Hyperthyroidism: In this condition, hepatic glucose output is increased along with the increase in glycogenolysis and this is the main cause for:

- hyperinsulinemia
- glucose intolerance
- Increase in peripheral insulin resistance.

In hyperthyroidism, the hepatic beta-oxidation and lipolysis are increased which may lead to ketoacidosis (Wang, 2013).

Hypothyroidism: In this condition, hepatic glucose output and glucose disposal are decreased. Glucose absorption from the gastrointestinal tract is reduced and gluconeogenesis process is delayed along with the prolonged peripheral glucose accumulation. In subclinical and overt hypothyroidism, insulin resistance causes glucose-stimulated insulin secretion. In addition, the physiological requirement of insulin is decreased because of the reduced in the renal clearance of insulin (Ray and Ghosh, 2016).

An investigation in sound euthyroid men indicated a positive correlation among TSH, endothelial dysfunction, and insulin resistance providing additional proof to the three-way connection between thyroid condition, insulin resistance and the risk of cardiovascular diseases. Thyroid hormones increase circulating fatty acids, by stimulating the action of catecholamine on adipose tissues and lead to increase lipolysis. This is confirmed by a remarkable increase in gluconeogenesis in T3 treated animal through increase amount of circulating fatty acid concentration along with an increased availability of gluconeogenic substrate from peripheral sources (Ray and Ghosh, 2016).

Thyroid hormone and hepatic insulin resistance

An elevated level of thyroid hormones is related to; more hepatic glucose synthesis; reduce glucose tolerance and hepatic insulin resistance. Insulin is secreted by beta pancreatic cells. Glucose hemostasis in the human body is regulated by insulin and metabolism of glucose by insulin-sensitive tissues such as muscles and liver. Insulin decreases hepatic glucose production and opens the door for glucose to utilize in peripheral tissues. Insulin resistance is related to obesity, T2DM and predisposes affected individuals to glucose intolerance.

Thyroid hormones can increase inappropriate hepatic glucose production during insulin resistance and stimulate lipogenesis during hyperinsulinemia. The correlation between thyroid receptors signaling and glucose metabolism is due to the stimulation of ChREBP by thyroid hormone. ChREBP is a transcription factor that causes the stimulation and the expression of the enzymes, which increase the synthesis of lipids in response to insulin and glucose (Sinha *et al.*, 2014).

Effects of diabetes mellitus on thyroid disorders

In diabetic patients having a normally functioning of the thyroid gland, the glycemic status causes alteration in the serum T3 (Tri-iodothyronine) levels, TSH concentration, and the response of TSH to TRH. Diabetes mellitus effects on thyroid function at two sites, first TSH release which is controlled by the hypothalamus, poorly controlled diabetes result in an impaired response of TSH to TRH or loss of TSH nocturnal peak. Second conversion of T4 to T3 which occur in the peripheral tissue. Diabetes is characterized by hyperglycemia which causes reversibly decrease in the hepatic concentration and activity of T4-5-deiodinase enzyme, decrease T3 serum concentration, increase the level of reverse T3 and normal, low or high level of T4 (Ray and Ghosh, 2016).

Rai *et al.* (2010-2012) conducted a study on 75 individuals aged 40-70 years to compare thyroid hormones levels, glycosylated hemoglobin, serum creatinine, and urine macroglobulin between T2DM patients without any complication and T2DM subjects with nephropathy. The study showed that in T2DM subjects without any complication and T2DM subjects with nephropathy there were decreased in the serum concentration of T3 and T4, and increased in the serum concentration of TSH as compared to controls. Increased levels of circulating insulin accompanied by insulin resistance, which has found to have a proliferative effect on thyroid tissues that may lead to increase thyroid size and nodule formations. The efficacy of the thyroid hormone therapy in a hypothyroid diabetic patient is affected by diabetes. The co-existence of diabetes with Graves' disease in the patients increases the incidence of optic neuropathy (Srinidhi Rai *et al.*, 2013).

Prevalence of thyroid disorders in diabetic patients

The prevalence of thyroid disorders in diabetic patients has been determined 10.8%, with the most common disorders occurring as hypothyroidism, subclinical hypothyroidism, hyperthyroidism and postpartum thyroiditis. Thirty percent of the female type 1 diabetic patients have thyroid disorders. The rate of postpartum thyroid disease is three times more than the normal population. This may be associated with estrogen and progesterone and patients who had one organ-specific autoimmune disease are at risk of developing other autoimmune disorders. Several other studies evidenced that the prevalence of thyroid disease in type 2 diabetes is higher than in the general population (Johnson, 2006). Ashok Khurana *et al.* (2016) conducted a study to find out the prevalence of thyroid disorder in type 2 diabetes mellitus. Total 200 patients with type 2 diabetes mellitus whom age was 40-70 years and examined for thyroid profile (T3, T4, and TSH). The result showed a high prevalence (16%) of thyroid disorder in type 2 diabetes mellitus patients. Subclinical hypothyroidism was the most common (7.5%), and more cases were found in females, aged patients, and those patients whose BMI was > 30 or patients on insulin, as well as uncontrolled diabetes, i.e., the HbA1c value is ≥ 7 . No significant relation of, duration of diabetes, dyslipidemia, family history of thyroid disorder and hypertension was seen with the prevalence of thyroid disorders (Khurana *et al.*, 2016; Jayaswal *et al.*, 2018).

Another study conducted by Priti Singh *et al.* (in Nepal in 2014) to evaluate the prevalence of thyroid dysfunction in type 2 diabetic patients in western Nepalese population. The

result showed the significantly lower level of FT3 and FT4 while the level of TSH was significantly higher in type 2 diabetic patient as compared to non-diabetics. Out of 100 diabetic patients evaluated, 29% showed abnormal thyroid hormone level, 24 percent hypothyroidism, and 5 % hyperthyroidism (Singh *et al.*, 2014).

Vikram B Vikhe *et al.* (2013), conducted a study to assess the prevalence of thyroid dysfunction in a patient with type 2 diabetes mellitus on 100 patients (50 diabetic and 50 nondiabetics) who attended outpatient department and medical ward in Dr. D Y Patil Medical College and Hospital. All the subjects were evaluated for thyroid profile (T3, T4, and TSH), Fasting Blood Sugar (FBS), glycosylated hemoglobin (HBA1c), serum cholesterol, serum triglycerides, HDL, LDL, VLDL, blood urea and serum creatinine. It was found that in type 2 diabetic patient the prevalence of thyroid dysfunction is very high. Out of 50 diabetic patients evaluated 30% had an abnormal level of thyroid hormones (8% had hyperthyroidism and 22% had hypothyroidism). In diabetic patients, the levels T3 and T4 were notably lower while that of TSH was significantly high as compared to nondiabetic patients. Similarly, a higher level of HBA1c, FBS, serum triglyceride, serum cholesterol, LDL, VLDL, blood urea, creatinine, and lower level of HDL was seen in diabetics as compared to nondiabetic patients (Vikhe *et al.*, 2013).

Guillermo E *et al.* conducted a longitudinal study to find out the natural history of thyroid dysfunction in patients with type 1. They analyzed the occurrence of thyroid dysfunction in 58 patients (26 men and 32 women) who enrolled in the Diabetes control and complication Trial at the University of Tennessee Health Science Center in 1983 and followed for 18 years. Patients were investigated for thyroid function test (T3, T4, and TSH) every year and thyroid peroxidase (TPO) antibodies at the interval of four years. As a result, it was found that a total 18 patients out of 58 had hypothyroidism, and 1 patient experienced with transient hyperthyroidism. The mean age of diagnosis for hypothyroidism was 29 ± 3 years and 19 ± 2 years for type 1 diabetes. Hypothyroidism was more common in female (41%) than in male (19%). Patients positive for TPO antibodies were found more susceptible to develop hypothyroidism as compared to those patients who were TPO negative. No variation was found in BMI, lipid profile, and HBA1C between the patients with and without thyroid dysfunction (Umpierrez *et al.*, 2003).

Conclusion

Thyroid disorders are more common in diabetic patient as compare to the non-diabetic individuals. Hypothyroidism is more prevalent thyroid disorder in the adult population and is more common in women than men. In diabetic patients, the thyroid function level changes, and abnormal thyroid hormone level in the diabetic patient cause poor management of diabetes, which is evidenced in some treated diabetics. The association between diabetes and thyroid disorder was found to be significant. By considering this association and interdependence of this two condition, evaluation of thyroid hormone level along with the diabetic profile in the early stage of diabetes will not only help in the management of diabetes but it will also delay and avoid the progression of the secondary complications in diabetic patients, particularly those with uncontrolled diabetes. In addition; it will improve

the quality of life and decrease morbidity and mortality rate in diabetic patients. Therefore, the diabetic patient should be screened for thyroid dysfunction as frequent as possible, preferably every 1 year for T1DM and every five years for T2DM.

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