

**Original article:**

## **A study of complications of diabetes mellitus and their association with thyroid disorder in patients with Type 2 Diabetes**

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**Abstract: -**

**Background:** Diabetes mellitus is a complex multifactorial disease with varying aetiologies but in most of the cases there is genetic predisposition. A plethora of preclinical, molecular and clinical studies have evidenced an undeniable role of thyroid malfunctioning as a comorbid disorder of T2DM.

**Aims and Objective:** To know the prevalence of thyroid dysfunction in diabetes mellitus type 2 and association of thyroid disorders with complications of type 2 diabetes mellitus. **Materials and Methods:** A cross sectional study was conducted in type 2 diabetic patients coming in OPD and IPD of medicine department. A total of 234 patients were included in the study based on inclusion and exclusion criteria. Patients were explained about the nature of the study and consent was obtained. Clearance was taken from the ethics committee. All participants were subjected to detailed clinical examination and relevant investigation. Chisquare test was used for the analysis.

**Results:** Two hundred and thirty-four patients, 112 males and 122 females were included in the study. The mean body mass index was high ( $26.21 \pm 3.13$  kg/m<sup>2</sup>). Thyroid dysfunction was found in 84 cases (35.8%), out of which the most common thyroid abnormality was overt hypothyroidism (61.9%) followed by subclinical hypothyroidism (27.3%). Overt hypothyroidism was found in diabetic patients with complication of neuropathy (3 patients, 6.39%), Retinopathy (13 patients, 19.69%) and nephropathy (13 patients, 33.3%).

**Conclusions:** The study shows a high prevalence of thyroid dysfunction among patients with T2DM and its association with poor glycemic control. Out of all complication of type 2 DM, diabetic nephropathy was associated with autoimmune thyroid disorders.

**Keywords:** Diabetes, thyroid dysfunction, Neuropathy, Retinopathy, Nephropathy, Hypothyroidism

### **Introduction**

Diabetes mellitus (DM) and thyroid dysfunction (TD) are endocrinopathies that are commonly seen in routine practice, and they frequently coexist. A high prevalence of TD is seen among both type 1 (T1DM) and type 2 (T2DM) diabetes mellitus patients [1, 2]. Autoimmunity can explain the common linkage between T1DM and autoimmune thyroid diseases; however, the linkage between T2DM and TD is more complicated. This review summarizes current knowledge about coexistent T2DM and TD and discusses enhanced screening recommendations as well as clinical implications for the management of these two endocrinopathies. According to the International Diabetes Federation (IDF), in the year 2017, approximately 425 million adults worldwide were living with diabetes [3]. The total prevalence of diabetes is increasing and is expected to be 629 million by

2045 [3].As per a large European meta-analysis, TD is present in 3.82% of the general population [4]. Its prevalence among those with T2DM is significantly higher, ranging from 9.9 to 48% [5, 6]. In many studies, most T2DM patients with TD had subclinical hypothyroidism (SCH), and several new cases of TD were diagnosed during clinical evaluations, highlighting the need for enhanced screening for TD in T2DM patients [5, 7, 8].The prevalence of subclinical and overt hyperthyroidism in India is 1.6% and 1.3%[9].Altered thyroid hormones have been described in patients with diabetes especially those with poor glycemic control. The first report showing the association between diabetes and thyroid dysfunction were published in 1979[10,11]. Subclinical hypothyroidism can exacerbate the coexisting dyslipidemia commonly found in type 2 diabetes mellitus (T2DM) and further increase the risk of cardiovascular diseases. Autoimmunity has been implicated to be the major cause of thyroid- dysfunction associated diabetes mellitus. This study aimed to know the prevalence of thyroid dysfunction, including autoimmune thyroid disease, in diabetes mellitus type 2 and association of thyroid disorders and complication of type 2 diabetes mellitus.

### **Material and Methods**

A cross sectional study was conducted in Department of Medicine, SP Medical College and associate hospital Bikaner. Study duration was 6 months from July to December 2020. A total of 234 patients from OPD and IPD of medicine department was included in the study. The inclusion criteria of study were age more than 40 years with type 2 diabetes mellitus and exclusion criteria were patients having type 1 diabetes, pregnant women, who are under Intensive care, previous history of thyroid surgery, preexisting connective tissue disorder, on insulin therapy and not willing to participate in study. All patients underwent clinical evaluation, followed by laboratory evaluation. The following clinical variables were documented: gender, age (years), duration of DM (years), body mass index (BMI), blood pressure (systolic and diastolic), monofilament test, ankle brachial index, goiter, acanthosis nigricans, and ankle jerk. Retinopathy staging was done as per Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group diabetic retinopathy classification system. Blood samples were obtained for biochemical analysis: HbA1c, lipid profile, creatinine, free thyroxine (FT4) and thyrotropin (TSH), anti-thyroperoxidase antibody (anti-TPO), urine for the albumin-creatinine ratio (ACR). . HBA1c was measured by high-pressure liquid pressure chromatography Biorad D10 method. Serum TSH, FT4, and anti-TPO were estimated by the electrochemiluminescence technique using commercially available kits from Siemens Diagnostics (Mannheim, Germany) with Immulite 1000 analyzer. The analytical sensitivity and total precision values for TSH and FT4 assays were 0.004  $\mu$ IU/ml and 2.2%, 0.35 ng/dl and 2.7%, respectively. The laboratory reference ranges were TSH (0.4–4  $\mu$ IU/ml) and FT4 (0.8–1.9 ng/dl) and the inter-assay coefficients of variation (CV) for the assays were 8.9% and 5.5%, respectively. Confidentiality was maintained at each and every step. The study was approved by institutional ethical committee. Informed consent was taken from the patients/ guardian after which consent, they were accessed for various risk factors. Statistical analysis was performed with IBM SPSS Statistics version 21 Software. p-value less than or equal to 0.05 was considered as significance.

### **Results**

This study was conducted at the Department of General Medicine, Sardar Patel Medical College and PBM Hospital Bikaner. Total of 234 cases of T2DM were selected following the inclusion and exclusion criteria. All the cases were subjected to a thorough history, clinical examination and laboratory investigations. In the present study, age of the patients were varied from 40 years to 85 years with maximum number of patients (112 males

and 122 females) were observed in the age group 51- 60 years (Table 1). The mean ages of the patients were  $58.18 \pm$

10.08. Out of 234, maximum number cases 106 (45.30%) had a BMI of 25 - 29.9 kg/m<sup>2</sup> and 96 (41.02%) case in the range of 18 – 24.9 kg/m<sup>2</sup>. The mean BMI of T2DM cases was high as  $26.21 \pm 3.13$  kg/m<sup>2</sup> (Table 2). Maximum numbers of cases 89 (38.03%) were having of T2DM for duration of 6 – 10 years followed by 61 (26.06%) cases of duration <1 years. The mean duration of T2DM was  $8.42 \pm 4.18$  years (Table 3). The mean value of HbA1c was  $8.81 \pm 1.96\%$ . The mean value of FBS was  $126.31 \pm 29.76$  mg/dl and of PPBS  $216.29 \pm 52.82$  mg/dl. Out of 234 patients, maximum numbers (66 cases) of cases were having retinopathy, 47 cases were having neuropathy and 39 cases were having nephropathy. There were 36 cases who were having both retinopathy and nephropathy (Table 4). It was observed that Total T3 and Total T4 value were  $1.04 \pm 0.78$  (95%CI 0.1-3.80) Pmol/L and  $6.66 \pm 3.17$  (95%CI 0.42 – 15.20) Pmol/L respectively. The TSH value of cases was  $9.96 \pm 7.45$  (95% CI 0.24 – 100.0) mIU/L. Normal thyroid function was observed in 64.10% cases of T2DM and 22.22% cases were overt hypothyroidism, 9.83% cases were sub clinical hypothyroidism, 1.28% cases secondary hypothyroidism and 2.56% cases were hyperthyroidism (Table 5). The patients with complication of nephropathy, neuropathy and Retinopathy also had associated thyroid disorders. Overt hypothyroidism was found in diabetic patients with complication of neuropathy (3 patients, 6.39%), Retinopathy (13 patients, 19.69%) and nephropathy (13 patients, 33.3%). 3 patients having retinopathy showed hyperthyroidism. Sub clinical hypothyroidism was found in patients with complication of retinopathy (4 patients) and Nephropathy (5 patients) (Table 6). The association between anti thyroid disorders and Diabetic Nephropathy and Peripheral neuropathy was found to be statically significant. (chi square test- 72.001, p value 0.001) While association between Thyroid disorder and Retinopathy and other macrovascular complications in type 2 diabetes was not found to be statistically significant.

## Discussion

Among the endocrinal metabolic diseases, diabetes occupies the major share. It has been associated with various physiologic changes in different organ systems of human body. The varying complications are associated with the morbidity and mortality associated with diabetes. {12} This study was conducted in 234 type 2 diabetic patients reached to medicine OPD and PD for various reasons.

In this study, age of the patients were varied from 40 years to 85 years with maximum number of patients were observed in the age group 51- 60 years. The mean ages of the patients were  $58.18 \pm 10.08$ . This finding was comparable with various studies conducted in different region of country. 18-23 In present study 47.86% patients were male and 52.14% patients were female.

Out of 234, maximum number cases 106 (45.30%) had a BMI of 25 -29.9 kg/m<sup>2</sup> and 96 (41.02%) case in the range of 18 – 24.9 kg/m<sup>2</sup>. The mean BMI of T2DM cases was high ( $26.21 \pm 3.13$  kg/m<sup>2</sup>). In different studies, sufficient numbers of T2DM cases were seen with high BMI. {13,14} A variety of intervention studies show that patients with T2DM who succeed in losing weight often enjoy modest improvements in glycaemic control and cardiovascular risk profiles, as long as the weight loss is maintained. {15}

It was observed that Total T3 and Total T4 value were  $1.04 \pm 0.78$  Pmol/L and  $6.66 \pm 3.17$  Pmol/L respectively. The TSH value of cases was  $9.96 \pm 7.45$  mIU/L. The mean TSH value was higher in study group probably because in diabetic patients, the nocturnal TSH peak is blunted or abolished and the TSH response to TRH is impaired. {16}

In 1978, Saunder J et al {17} reported that the metabolic clearance of glucose is directly proportional to circulating T3 and inversely to rT3. Many studies reported Lower T3 level in diabetic patients as compared to control patients.{18-22} Various studies conducted in different part of India showed mean FT3 and FT4 levels in T2DM cases were low as compared to control population.18 Similarly many studies mentioned that T3 and T4 was relatively low and TSH was reported high in diabetic patients as compared to control.{23-27}

In this study maximum 64.10% cases of Type 2 DM were normal thyroid function and 22.22% cases were overt hypothyroidism, 9.83% cases were sub hypothyroidism, 1.28% cases secondary hypothyroidism and 2.56% cases were hyperthyroidism. Kiran Babu et al{22} reported 28% of thyroid dysfunction in T2DM case with 13.2% having hypothyroidism, 8.8% having hyperthyroidism and low T3 syndrome in 5.8%. Celani M F et al40 reported 31.4% thyroid dysfunction in T2DM cases. Out of these, Subclinical hypothyroidism was most common (48. 3%), followed by subclinical hyperthyroidism (24. 2%) and by definite hypothyroidism (23. 1%). Definite hyperthyroidism was found in 4 patients (4. 4%).

Insulin resistance has been shown to be caused in hypothyroidism in various in vitro and preclinical studies where it was found that peripheral muscles became less responsive in hypothyroid conditions. A possible role of dysregulated metabolism of leptin has been implicated for such pathology.{28}

Insulin resistance and cell function are inversely correlated with TSH which may be explained by insulin-antagonistic effects of thyroid hormones along with an increase in TSH. The higher serum TSH usually corresponds to lower thyroid hormones via negative feedback mechanism. As TSH increased, thyroid hormones decreased and insulin antagonistic effects are weakened. These observations demonstrate that insulin imbalance is closely associated with thyroid dysfunction and the phenomenon is mediated via cell dysfunction (T2DM){28}. Thyroid disorder was associated with worsening of glycemic status (p value <0.05) in patients with Type 2 diabetes. Also the association of thyroid disorder with complications of type 2 diabetes especially diabetic nephropathy and peripheral neuropathy was found to be statistically significant (p value <0.05), suggesting that thyroid dysfunction in Diabetic patients leads to poor glycemic control and increased microvascular complication which can be improved or prevented with timely diagnosis and optimal treatment. The limitation of study was low sample size. A larger sample size with extended duration of study could provide some better results.

### **Conclusion**

A holistic approach is required for optimal treatment of Type 2 Diabetes and to prevent micro or macrovascular complications and status of thyroid function is a very important component. In this study we found that association of thyroid dysfunction in diabetes leads to poor glycemic control and increased complications. Further prospective studies are required to determine the improvement in these parameters after optimal treatment of thyroid dysfunction.

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