ORIGINAL ARTICLE

THYROID DYSFUNCTION AMONG TYPE 2 DIABETICS AND NON-DIABETICS: A CASE CONTROL STUDY

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Background: Type 2 diabetes mellitus (T2DM) and thyroid disorders are most commonly encountered endocrinal disorders. The objective of this study was to evaluate thyroid dysfunction among type 2 diabetics and non-diabetics. **Methods:** This case control study was conducted for 6 months from Jul to Dec 2023, and patients were included through non-probability convenient sampling technique. Patients were divided into two groups (150 type 2 diabetics and 150 non-diabetics). Diagnosed cases of type 2 diabetes confirmed by using ADA criteria for minimum 6 months were included. Patients with diabetic ketoacidosis, chronic renal failure or using drugs affecting thyroid functions were excluded. SPSS-23 was used for data analysis. Independent *t*-test was applied and $p<0.05$ was considered statistically significant. **Results:** Total 49.3% of patients were diabetic for 1–5 years. Mean serum T_3 was 110.4±40.74 ng/dL in diabetic group and 154.7±11.35 ng/dL in non-diabetic group ($p<0.001$). Mean serum T_4 level was 6.89±2.90 µg/dL in diabetic group and 8.76±0.94 µg/dL in non-diabetic group ($p<0.01$). Mean TSH level was 7.44±7.29 mIU/mL in diabetic group and 2.73±1.67 mIU/mL non-diabetic group ($p<0.0001$). Mean HbA1c was 7.49±0.84% in diabetic group and 5.78±0.51% in non-diabetic group ($p<0.001$). **Conclusion:** Diabetic patients were at a higher risk for thyroid dysfunction. Significantly lower level of T_3, T_4, and higher levels of TSH were reported among diabetics, compared to non-diabetics. Subclinical hypothyroidism was the most frequently reported thyroid disorder.

Keywords: Type 2 diabetes, T2DM, Thyroid dysfunction, Hypothyroidism, Subclinical

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a significant public health burden, affecting over 422 million people globally, and its prevalence is expected to continue rising due to lifestyle factors and demographic changes. The interplay in-between thyroid dysfunction and type 2 diabetes is complex and multifaceted, with both conditions sharing common risk factors and pathophysiological mechanisms.[1]

The coexistence of thyroid dysfunction, encompassing hypothyroidism, hyperthyroidism, and autoimmune thyroid diseases, alongside T2DM, has been increasingly recognized in clinical practice.[2] This intersection not only poses diagnostic challenges but also underscores the potential bidirectional influence these conditions may exert on each other's pathogenesis and management.[3]

Type 2 diabetes mellitus, characterized by relative insulin deficiency and/or insulin resistance, has reached epidemic proportions globally, emerging as a major public health concern.[4] With its multifactorial aetiology involving genetic predisposition, lifestyle factors, and environmental influences, T2DM manifests with a spectrum of metabolic abnormalities that extend beyond glycaemic dysregulation.[5] Among these, alterations in thyroid function have emerged as noteworthy associations, drawing attention to the intricate interplay between metabolic and endocrine pathways.[6]

Thyroid dysfunction, encompassing both hypo- and hyperthyroidism, represents a spectrum of disorders characterized by aberrations in thyroid hormone production or action.[7] Hypothyroidism, marked by insufficient thyroid hormone synthesis, and hyperthyroidism, characterized by excessive thyroid hormone secretion, poses distinct clinical challenges.[8] Autoimmune thyroid diseases, including Graves' disease and Hashimoto's thyroiditis, further complicate the landscape by introducing an immune-mediated component to thyroid dysfunction.[9]

Conversely, the metabolic milieu associated with T2DM, characterized by insulin resistance, dyslipidemia, and chronic inflammation, may exert profound effects on thyroid function. Insulin resistance, a hallmark of T2DM, has been implicated in the pathogenesis of thyroid disorders through mechanisms involving altered thyroid hormone synthesis, secretion, and peripheral metabolism.[10] Thyroid stimulating hormone (TSH) stimulates leptin secretion in adipose tissue and exerts important role on hepatic glucose metabolism. Moreover TSH reduces insulin secretion from beta cells of pancreas. Leptin is neuro-endocrine regulator of hypothalamic-pituitary-thyroid axis and is involved in secretion of TRH by regulating expression of TRH gene. Leptin levels correlate with TSH levels and

are elevated in hypothyroidism. Thyroid hormones have insulin antagonistic effects on liver. Glucose intolerance in patients with hyperthyroidism is primarily caused by hepatic insulin resistance, as excess thyroid hormone increases endogenous glucose production, raises insulin demand, and decreases hepatic insulin sensitivity. Excess thyroid hormone promotes β-cell apoptosis, which may play a significant role in the worsening of glucose tolerance in thyrotoxicosis, leading to hyperglycaemia. In hyperthyroidism, peripheral glucose transport and tissue utilization are elevated, accompanied by peripheral insulin resistance.[7] Furthermore, dyslipidemia, commonly observed in individuals with T2DM, may influence thyroid hormone transport and metabolism, thereby modulating thyroid function.[10]

Research has shown that individuals with diabetes tend to be at higher risk of having thyroid dysfunction compared to those without diabetes.[11] A study found that incidence of thyroid dysfunction among individuals with type 2 diabetes was significantly higher compared to those without diabetes.[12] Another study reported that possibility of developing hypothyroidism was substantially higher in individuals having T2DM compared to non-diabetics.[13]

Although there is increasing evidence highlighting link between thyroid dysfunction and diabetes, there is a significant knowledge gap regarding incidence and characteristics of thyroid dysfunction among individuals with diabetes. There is need for more research on impact of thyroid dysfunction on management and outcomes of T2DM. This study aims to evaluate prevalence of thyroid dysfunction among individuals with T2DM and non-diabetics.

METHODOLOGY

This case-control study was conducted in the Outpatient Department (OPD) of General Medicine Department at Shahida Islam Teaching Hospital, Lodhran. The research was carried out for a period of 6 months from July to December 2023 and patients were selected through non-probability convenient sampling technique after obtaining Institutional Review Board Letter No. SIMC/ET.C./10007/23. Sample size was calculated using Open EPI software online by keeping prevalence of T2DM in Pakistani population as 26.7%[13]. Patients were divided into two groups (150 type 2 diabetics and 150 non-diabetics). Diagnosed cases of diabetes type 2 for minimum of six months were included. Diagnosis of diabetes was confirmed by using American Diabetic Association (ADA) criteria, i.e., a fasting blood glucose ≥126 mg/dL or random blood sugar ≥200 mg/dL.[14] Patients with diabetic ketoacidosis, chronic renal failure or using lithium and amiodarone drugs which affect thyroid disorders were excluded.

Five mL of venous blood was collected from patients to assess thyroid function tests T_3, T_4, TSH, fasting blood sugar, and HbA1c. The normal range for T_3, T_4 and TSH are tabulated as Table-1 as per Roche Chemiluminescent Immunoassay (CLIA) kit literature.[15]

Table-1: Reference range of thyroid hormones

Test	Normal value
TSH	0.3–4.0 mIU/mL
T_3	80–180 ng/dL
T_4	4.5–12.5 µg/dL

Assessment of T_3 and T_4 were done on Roche Chemistry analyzer using CLIA. TSH was assessed through Ultra-Sensitive CLIA method. The normal range taken for fasting blood sugar was 70–100 mg/dL and HbA1c below 5.70% according to ADA criteria.[14] Thyroid status was considered normal when all T_3, T_4 and TSH were within normal range. TSH levels >4 mIU/mL while T_3 and T_4 below normal were labeled as primary hypothyroidism. Primary hyperthyroidism is characterized by TSH levels <0.3 mIU/mL and higher than normal T_3 and T_4. When TSH was >4.0 mIU/mL while T_3 and T_4 were within normal limits, this was known as subclinical hypothyroidism. When TSH was <0.3 mIU/mL and T_3 and T_4 were within the normal range, this was known as subclinical hyperthyroidism.[15]

SPSS-23 was used for data analysis. Results were reported as frequency and percentages for qualitative variables, and discreet variables as Mean±SD. Independent *t*-test was applied to test for differences between both groups of type and diabetics and non-diabetics, and $p \leq 0.05$ was considered significant.

RESULTS

The total of 300 participants were grouped into two groups of 150 each, i.e., type-2 diabetics and age-comparable non-diabetic healthy participants. A total of 42% of patients in the diabetic group were male, compared to 46% in the non-diabetic group; 49.3% of diabetics had been diagnosed with type 2 diabetes within the past 1 to 5 years. Twenty-five percent of diabetic patients were aged 30–40 years, 28% were 41–50 years, 34.7% were 51–60 years, and 12% were in age group 61–70 years. Among the non-diabetic healthy group, 18.7% were aged 30–40 years, 29% were 41–50 years, 41.3% were 51–60 years, and 10.7% were 61–70 years old. A total of 18.7% patients in diabetic group had diabetes diagnosed for less than a year while 49.3% had diabetes for 1–5 years, while 32% suffered from diabetes for more than 5 years (Table-2).

Among the diabetic patients, 54 patients were diagnosed having some thyroid disorder with subclinical hypothyroidism observed in 27 (18%) patients, primary hypothyroidism in 19 (13%), while primary hyperthyroidism in 8 (5%) patients. A significant difference was observed between the thyroid function tests and glycosylated haemoglobin in diabetic versus non-diabetic group.

The mean level of serum T_3 in the diabetic group was 110.4±40.74 ng/dL while in non-diabetics mean level was 154.7±11.35 ng/dL (p<0.001). Mean serum T_4 levels in diabetic group were 6.89±2.90 µg/dL while in non-diabetics mean levels were 8.76±0.94 µg/dL (p<0.01). The mean TSH level in diabetic group was 7.44±7.29 mIU/mL while in non-diabetics mean TSH level was 2.73±1.67 mIU/mL (p<0.0001). Mean HbA1c among diabetics was 7.49±0.84 % while 5.78±0.51% in non-diabetic group (p<0.001). (Table-3).

Subclinical hypothyroidism was reported in 27 patients while primary hypothyroidism was reported in 19 patients and primary hyperthyroidism in 8 patients. In the non-diabetic group 17 patients were found having subclinical hypothyroidism, 4 were reported having subclinical hyperthyroidism while 2 were found having primary hyperthyroidism (Table-4).

Table-2: Baseline demographics of study participants [Frequency (%)]

Variables		Type 2 Diabetics (n=150)	Non-diabetics (n=150)
Gender	Male	63 (42)	69 (46)
	Female	87 (58)	81 (54)
Age (Years)	30–40	38 (25.3)	28 (18.7)
	41–50	42 (28)	44 (29.3)
	51–60	52 (34.7)	62 (41.3)
	61–70	18 (12)	16 (10.7)
Duration of diabetes (Years)	<1	28 (18.7)	--
	1–5	74 (49.3)	--
	>5	48 (32)	--

Table-3: Thyroid profile and glycosylated haemoglobin in study groups (Mean±SD)

Variables	Type 2 Diabetics n=150	Non-Diabetics n=150	p
Serum T_3 (ng/dL)	110.4±40.74	154.7±11.35	<0.001
Serum T_4 (µg/dL)	6.89 ±2.90	8.76±0.94	<0.01
Serum TSH (mIU/mL)	7.44±7.29	2.73±1.67	<0.0001
HbA1c (%)	7.49±0.84	5.78±0.51	<0.001

Table-4: Type of thyroid disorder among diabetic and non-diabetic groups [n (%)]

Groups	Subclinical Hypo-thyroidism	Primary Hypo-thyroidism	Subclinical Hyper-thyroidism	Primary Hyper-thyroidism
Diabetic	27 (18)	19 (13)	0 (0)	8 (5)
Non-diabetic	17 (11)	0 (0)	4 (3)	2 (1)

DISCUSSION

The study was done to evaluate thyroid dysfunction among diabetics. Similar findings to those observed in this study have been reported by others. They observed frequencies of thyroid disorders among diabetics ranging from 12.3 to 32.4%.[16] In our study frequency of thyroid disorder among diabetic patients was 36%.

Hypothyroidism in a study was reported in 22% of diabetics with 14% of patients among them being subclinical hypothyroid and 8% being primary hypothyroid.[17] Another study reported 16.3% diabetic patients suffering from subclinical hypo-thyroidism, 11.4% having hypothyroidism, 2% subclinical hyperthyroidism and 1.5% hyper-thyroidism.[18] Similar results were observed in our study as well where 18% diabetic patients were found to have subclinical hypothyroidism, 13% primary hypo-thyroidism and 5% primary hyperthyroidism.

A research on type 2 diabetics determined frequency of thyroid disorder and reported that higher incidence of females were observed with thyroid disorder. Among 288 patients, hyperthyroidism was seen in 13.2 % of diabetic patients, subclinical hypothyroidism in 6.6 % of patients while 80.2 % of diabetic patients were euthyroid. The study also showed that 41.3% of patients reported a diabetes duration of 5 to 10 years,[19] as compared to our study findings where 49.3% had been living with diabetes for 1 to 5 years, and 32% had a duration of more than 5 years. In another study[20] the majority of the patients were diagnosed with diabetes between 6–10 years as compared to our study where majority of patients, i.e., 49.3% have diabetes of 1 to 5 years duration. Yet another study reported that 48.3% of patients were found to have sub-clinical hypothyroidism, while 24.2% were followed by subclinical hyperthyroidism, 23.1% with definitive hypothyroidism and 4.4% with definite hyperthyroidism.[21] Another study among 1,310 diabetics reported 13.4% of patients with thyroid dysfunction.[22] Ghazali *et al*[23] found 10.8% of diabetic patients having dysfunctional thyroid gland. Bukhari *et al*[24] showed 17.4% patients with subclinical hypothyroidism which was almost similar to this study 18%. Definite hypothyroidism was seen in 8.5% patients as compared to 13% in this study. No patient with subclinical hyperthyroidism was seen in our study. However Bukhari *et al*[24], reported 5% patients and definite hyperthyroidism was seen in 6% as compared to 5% in this study.

Most studies have reported thyroid dysfunction mainly in females, which is in accordance to our study. This could be because of higher frequency of diabetes among females. Nonetheless, the diagnosis of thyroid dysfunction in diabetes can be difficult especially if a diabetic patient is hyperthyroid, since both diabetes and hyperthyroidism present with similar picture clinically, i.e., loss of weight, increased appetite, fatigue and irritability.[25] Uncontrolled diabetes can lower levels of T_3 and T_4 while increasing TSH levels thereby further complicating clinical picture of thyrotoxicosis. Diabetic nephropathy presenting with oedema can sometimes mimic hypothyroidism. Even some drugs that are used for management of diabetes can lead to dysfunctional thyroid gland. Because of increased risk for adverse cardiovascular events, nephropathy, retinopathy, dysfunction of thyroid in diabetes increases mortality in comparison to euthyroid diabetics, as has been reported in a meta-analysis where subclinical hypothyroid diabetic

patients were at a 1.49 times higher risk of mortality than non-diabetics.[26] Further studies are needed to see whether diabetics with thyroid dysfunction should be treated in the same manner as individuals with thyroid dysfunction who are otherwise healthy. It is recommended that treatment for thyroid dysfunction be initiated on an individual basis, prioritizing those with insulin resistance, dyslipidemia, and patients at higher risk for adverse cardiovascular events.

CONCLUSION

Diabetic patients were at a higher risk for thyroid dysfunction and substantially lower levels of T_3, T_4, while high levels of TSH were reported among diabetics, compared to non-diabetics. Subclinical hypothyroidism was the most frequently reported thyroid disorder. Undiagnosed thyroid dysfunction can lead to metabolic disturbances and increase the risk of mortality by triggering fatal cardiovascular and atherosclerotic events.

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SH: Result analysis and critical review
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AZ: Critical review and writing
ZF: Final review and editing

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