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Original Research Article

RISK FACTORS FOR THYROID DYSFUNCTION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS ASSOCIATION WITH DIABETIC COMPLICATIONS

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ABSTRACT

Background: Diabetes mellitus patients are prone to the development of thyroid disorders. Many studies on diabetic patients have shown the development of thyroid dysfunction over a period of time. Diabetic patients with hypothyroidism have an increased risk of cardiovascular disease. Timely detection of thyroid dysfunction in these patients is important. The objective of this present study was to assess frequency and risk factors for thyroid dysfunctions among patients with type 2 diabetes mellitus and to identify the association of thyroid dysfunction with complications in diabetic patients. **Materials and Methods:** This was a cross-sectional study conducted at 2 tertiary care teaching hospitals in north India. Two hundred thirty patients with type 2 diabetes mellitus attending the outpatient department without having a prior history of thyroid disease and chronic liver disease were recruited into the study. All subjects were examined for diabetes-related complications. **Results:** Mean age of study participants was 56.5 years. The mean duration of diabetes was 6.43 ± 1.92 years and the mean HbA1c was 9.4 ± 2.76%. The frequency of thyroid dysfunction was 16.08% among the study population. Hypothyroidism was more frequent than hyperthyroidism (13.04% vs 3.04%). Thyroid dysfunction was more common among females than males. On multivariate analysis, duration of DM <5 years had a greater chance of having thyroid dysfunction than the duration of DM ≥ 5 years (OR = 3.2, p = 0.00). Similarly, obesity (OR = 2.6, p = 0.00), HbA1c ≥7 (OR = 3.8, p = 0.00), and absence of diabetic foot ulcer (OR =3.7, p = 0.00) were risk factors for thyroid dysfunction. There was no association observed between thyroid dysfunction and other diabetic complications among the study participants. **Conclusion:** The study concluded that thyroid disorders are common among diabetic patients with hypothyroidism being commoner. A higher frequency of thyroid disorder was observed among diabetic patients who had a higher HbA1c, who were obese, and who had a more recent onset DM (<5 years duration). The frequency of thyroid disorder was lower among diabetic patients with foot ulcers whereas no association was observed between thyroid dysfunction and other microangiopathic complications of DM.

Keywords: thyroid dysfunction, type 2 diabetes mellitus, hypothyroidism, risk factors

INTRODUCTION

Thyroid dysfunctions may present either as hyperthyroidism or hypothyroidism and are diagnosed based on serum levels of thyroid-stimulating hormone (TSH) **(1, 2).** Thyroid dysfunction can present with thyroid enlargement; symptoms of thyroid hormone deficiency or excess or frequently may be asymptomatic **(3).** Disordered production of thyroid hormones may arise due to diseases of the thyroid gland itself or the pituitary gland (that produces TSH) or the hypothalamus [that controls the pituitary gland through Thyrotropin Releasing Hormone (TRH) **(4).**

Thyroid dysfunctions are quite common in the general population. Because of this, diabetes and thyroid diseases are frequently found to co-exist **(5, 6).** Patients suffering from DM may be at a higher risk of thyroid disease, particularly individuals having poor glycemic control. In diabetic patients, the nocturnal TSH peak is reduced or eliminated and the release of TSH in response to TRH secretion from the hypothalamus is diminished. This may lead to the development of hypothyroidism **(7).** In uncontrolled DM, low T3 levels are seen. It has been attributed to the inhibition of the peripheral conversion of T4 to T3 which often gets normalized with improvement in glycemic control **(5,8).** This occurs due to hyperglycemia-induced reversible reduction of the actions of thyroxine 5'deiodinase **(8).** Elevated levels of circulating insulin which is seen in type II DM have been shown to have a rapid multiplication effect on thyroid tissue which may result in enlargement of thyroid gland size with the formation of nodules **(5,9,10).** This may lead to the development of hyperthyroidism in diabetic patients. Metformin has been shown to decrease TSH levels in patients with hypothyroidism. Studies have revealed that patients with pre-diabetes and type 2 DM have a significant increase in thyroid volume and a higher prevalence of incident nodules and goiter **(11).** Many studies have evaluated the prevalence of thyroid dysfunction among diabetic patients, nonetheless only a few studies have evaluated the possible risk factors for thyroid dysfunction among diabetic patients. The objective of the present study was to assess frequency and risk factors for thyroid dysfunction among patients with type 2 DM and to identify the relation of thyroid dysfunction with the presence of complications among these diabetic patients.

MATERIALS AND METHODS:

This cross-sectional study was conducted at the OPDs of departments of Medicine IIMSR, Integral University, Lucknow and HIMS, Sitapur between June 2016 and May 2018. Ethical clearance was taken from the Institutional Ethics Committee. Assuming a prevalence of 16.2% for thyroid dysfunction among diabetic patients, based on a previous study, the sample size was calculated by the formula 4PQ/L2, where P is the prevalence; Q is 100-P and L is the absolute precision (5%). The sample size came out to be 230. A simple random sampling technique was used to include diabetic patients attending the Medicine OPDs of the hospital. Patients with already known thyroid disease, acute illness, and chronic liver disease were excluded from the study. All subjects were evaluated, using a pre-validated questionnaire. Demographic data of the study subjects were collected.

Operational definition: The neck was examined for the presence of an enlarged thyroid gland. Evaluation for the complications of DM was done in all patients. Fundoscopy was done with the help of an Ophthalmologist. The laboratory investigations that were conducted were glycosylated hemoglobin, fasting lipid profile, and urine albumin. Screening for diabetic retinopathy was done by fundus examination. The presence of peripheral neuropathy was detected using a tuning fork and tendon hammer. Anthropometric measurements such as height and weight were recorded using a standard scale and stadiometer from Lincoln Mark Medical England; waist and hip circumference were calculated using a measuring tape. Body Mass Index (BMI) was measured using the standard formula **(12,13).** Study population with BMI of between 18 to 25 kg/m2 were classified as normal, whereas those with a BMI of more than 30 kg/m2 were classified as obese **(14)**. Waist circumference (WC) was observed in centimeters (cm) using a standard procedure **(15).** As per International Diabetes Federation (IDF)'s guidelines, in males, WC of ≤94 cm was classified as normal, whereas WC of >94 cm was classified as abnormal. In females, WC of ≤80 cm was classified as normal whereas WC of >80 cm was classified as abnormal **(16).** Three consecutive pulse rates were taken from study subjects and their mean was recorded. Blood pressure (BP) was measured in the right arm in a sitting position with a mercury sphygmomanometer, after 5 minutes of rest **(17).** The 1st Korotkoff's sound (Phase I) was recorded as systolic BP and the last sound (phase V) as diastolic BP. The mean of three consecutive BP

recordings, taken 1 minute apart, was noted. Normal BP was defined as a systolic BP of <130 mmHg, and or diastolic BP of <80 mm Hg. If not, considered to have a high BP, in agreement with the American Diabetes Association (ADA) **(18).** Glycaemic control was assessed with the values of the HbA1c. HbA1c value was used to categorize the DM patients into good glycaemic control (HbA1c <7%) and poor glycaemic control (HbA1c ≥7%) groups.

Diabetes mellitus: Diagnosis of DM was based on impaired fasting blood glucose (FBG) or Impaired Glucose Tolerance Test (GTT). The cut-offs used, were from the 1997 ADA fasting glucose criteria (FPG) and the WHO oral glucose tolerance test criteria **(19).** Thus, by the FPG criteria, values of >7.0 mmol/l (126 mg%) and 6.1-6.9 mmol/l (111-125 mg%) were taken diabetes and IFG respectively, and by the 2hrs post-glucose criteria, values > 11.1 mmol/l (>200 mg%) and 7.8- 11.0 mmol/l (140-199 mg%) were taken diabetes and IGT, respectively.

Overt hypothyroidism/ Subclinical hypothyroidism: Cases were diagnosed to have overt hypothyroidism if the level of TSH was >4.50 µIU/mL, fT4 was < 0.8–1.8 ng/dL and fT3 was < 1.4–4.4 pg/mL **(20),** using criteria from published studies for the diagnosis of Thyroid Dysfunction. **(21-25)**

Statistical Analysis: The data was analyzed using the Statistical Package for the Social Sciences (SPSS) IBM version 16.0. Quantitative variables like age, duration of diabetes, HbA1c, BMI, waist circumference, weight, height, systolic BP, diastolic BP were presented as a mean and standard deviation; the Chi-square test was used for comparison of proportions. P < 0.05 was considered statistically significant.

RESULT:

A total of 230 participants were recruited in this study. The baseline characteristics of the study subjects are given in Table 1. The mean duration of diabetes was 6.43 ± 1.92 years and the mean HbA1c was 9.4 ± 2.76%. The mean age of study participants was 56.5 ± 8.3 years. The mean BMI was 26.1 ± 4.7kg/m2. Mean systolic BP and diastolic BP (in mmHg) were 129.1± 19.6 and79.2± 10.1 respectively.

Table 1: Baseline features of the study population

Parameter	Mean	Standard deviation
Mean age (years)	56.5	8.3
Duration of diabetes (years)	6.43	1.92
HbA1c (%)	9.4	2.76
BMI (kg/m2)	26.1	4.7
Waist circumference (cm)	91.2	13.4
Weight (kg)	69.0	13.1
Height (m)	1.59	1.1
Systolic BP (mmHg)	129.1	19.6
Diastolic BP (mmHg	79.2	10.1

Table 2: Thyroid function test results of the study population

	Parameter		
Test results value	**Serum TSH N (%)**	**fT3 N(%)**	**fT N (%)**
Normal	193 (83.91)	201(87.39)	210(91.30)
Increased	30 (13.04)	2(0.87)	11(4.78)
Decreased	7(3.04)	27(11.74)	9(3.91)

Table 2 shows the result of the thyroid function test in the study subjects. A majority of study subjects had normal TSH, fT3, and fT4 values. Hypothyroidism (increased TSH) was observed in 13.04% while hyperthyroidism was observed in only 3.04% of the subjects. Overall, 16.08% of the study population was observed to have thyroid dysfunction.

Table 3: Univariate analysis of the probable risk factors of thyroid dysfunction

Variables			Thyroid Dysfunction Yes, n= 37	No, n=193	Chi square, p-values
Gender	**Male**	**n**	11	54	
		%	29.73	27.98	0.05,
	Female	**n**	26	139	0.82
		%	70.27	72.02	
Age (in years)	**<30**	**n**	1	13	
		%	2.70	6.74	1.02,
	30-50	**n**	15	69	0.59
		%	40.54	35.75	
	≥50	**n**	21	111	
		%	56.76	57.51	
Duration of DM (years)	**<5**	**n**	29	99	9.22,
		%	78.38	51.30	0.00*
	≥5	**n**	8	94	
		%	21.62	48.70	
HbA1c (%)	**≥7**	**n**	24	90	
		%	64.86	46.63	4.12,
	<7	**n**	13	103	0.04*
		%	35.14	53.37	
Hypertension	**Yes**	**n**	18	105	
		%	48.65	54.40	0.41,
	No	**n**	19	88	0.52
		%	51.35	45.60	
Obesity	**Yes**	**n**	25	70	
		%	67.57	36.27	12.54,
	No	**n**	12	123	0.00*
		%	32.43	63.73	
Nephropathy	**Yes**	**n**	14	55	
		%	37.84	28.50	1.28,
	No	**n**	23	138	0.25
		%	62.16	71.50	
Retinopathy	**Yes**	**n**	13	97	
		%	35.14	50.26	2.84,
	No	**n**	24	96	0.09
		%	64.86	49.74	
DM foot ulcer	**Yes**	**n**	3	43	
		%	8.11	22.28	3.89,
	No	**n**	34	150	0.04*
		%	91.89	77.72	

Table 3 shows that the association between risk factors and the presence of thyroid dysfunction. Females outnumbered males, accounting for 165, out of which 26 had thyroid dysfunction. The majority

of thyroid dysfunction patients were older than 50 years. There was no statistically significant difference in the frequency of thyroid disorder based on gender, age, presence of hypertension, nephropathy, and retinopathy. Thyroid dysfunction was found to be more frequent among subjects with

A shorter duration of DM (<5 years), poorly controlled DM (HbA1c > 7.0), and obese diabetic patients as compared to non-obese. Patients with diabetic foot ulcers were found to have a lower prevalence of thyroid dysfunction in the present study.

Table 4: Binary logistic regression risk factors of thyroid dysfunction

Variable	Subgroup	OR	Regression coefficient	95% CI		P-value
Duration of DM (years)	**≥5**	Reference	−1.03	1.4	6.9	0.00*
	<5	3.2				
HbA1c (%)	**≥7**	Reference	0.9	2.2	7.9	0.00*
	<7	3.8				
Obesity	**Yes**	Reference	−1.6	0.9	4.5	0.00*
	No	2.6				
DM foot ulcer	**Yes**	Reference	1.57	2.2	10.5	0.00*
	No	3.7				

Table 4 shows the results of multivariate analysis for thyroid dysfunction and its risk factors. Duration of DM (years), HbA1c (%), obesity, and DM foot ulcer were independently associated with thyroid dysfunction. Multiple logistic regressions were applied to detect the independent association of factors. Thyroid dysfunction present and absence are taken as the dependent variable. As shown in Table 4, the duration of DM <5 years had a greater chance of having thyroid dysfunction than the duration of DM ≥ 5 years. Similarly, obesity (OR = 2.6, p = 0.00), HbA1c ≥7 (OR = 3.8, p = 0.00), and absence of diabetic foot ulcer (OR =3.7, p = 0.00) were risk factors for thyroid dysfunction.

DISCUSSION:

Insulin resistance which is typically seen among patients with type 2 diabetes mellitus plays a major role in the development of thyroid dysfunction in them. Thyroid dysfunction can occur in the form of hypothyroidism and hyperthyroidism. Subclinical hypothyroidism can also occur in diabetic patients and can contribute to diabetic complications like retinopathy, neuropathy, and cardiovascular disease **(26).**

The frequency of thyroid dysfunction among type-2 DM patients in the present study was found to be 16.08%. Hypothyroidism was more frequent than hyperthyroidism among the study subjects. Similar findings were reported in south India by Jali MV et al. that found the prevalence of thyroid dysfunction in diabetic patients to be 16.2% **(27).** Another north Indian study had observed the prevalence of sub-clinical hypothyroidism to be 18.8% among diabetic patients. This study also found that females have a higher prevalence of thyroid dysfunction. A retrospective study was done by Demitrost L et al. observed that hypothyroidism was found in 11.4% of type 2 diabetic patients while hyperthyroidism was found in only 1.5% of the patients **(28).** A study, conducted by Diez et al, to evaluate the frequency of thyroid dysfunction in patients with type 2 DM reported that 15.1% of the patients suffered from overt hypothyroidism whereas subclinical hyperthyroidism was found in 3.5% of these diabetic patients **(29).**

Diabetic retinopathy was observed in 47.8% of the subjects in the present study. This finding was similar to the 42.1% incidence of retinopathy in a study by Ashaye et al **(30)**. Diabetic nephropathy was observed in 30% of the patients in this study. In contrast, Ulasi et al. observed 16.6 percent **(31).** In the present study, the presence of diabetic retinopathy and nephropathy were not found to be predictors for the presence of thyroid dysfunction.

The present study reported that risk for thyroid disorders was higher in subjects with a shorter duration of DM (less than 5 years) (OR = 3.3, p = 0.012). This is in contrast to the findings from previous studies which have shown that increasing duration of DM may be a risk factor in the prevalence of thyroid dysfunction **(32).** However, the study by Diez et al. found no significant relationship between the presence of thyroid dysfunction and the duration of DM. Similar to the present study, their study found thyroid dysfunction was not associated with the duration of diabetes, glycosylated hemoglobin, and the existence of diabetic complications **(29).** In contrast, another study conducted in Egypt observed a higher frequency of thyroid disorders in patients with a raised glycosylated hemoglobin **(33)**.

CONCLUSION:

The frequency of thyroid dysfunction was 16.08% among patients with type 2 diabetes mellitus with hypothyroidism being more frequent (13% Vs 3 %). The frequency of thyroid dysfunction was higher among those with a higher HbA1c, obesity, a short duration of DM (<5 years), and less frequent among those with diabetic foot ulcers. There was no association of thyroid dysfunction with other microangiopathic complications of DM as neuropathy, retinopathy, or nephropathy in the present study.

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