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Original Article

Association of Subclinical Hypothyroidism in Type 2 Diabetic Individuals

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Abstract

Background: Diabetes Mellitus and Thyroid Disorders, both ranks as most prevalent endocrine diseases in clinical practice for last several years. Thyroid hormones play a pivotal role in various metabolic pathways, including carbohydrate metabolism.
Objective: The association and prevalence of subclinical hypothyroidism in type 2 diabetic patients was assessed.
Study type, settings & duration: This case control study was conducted at National Medical Center Hospital, Karachi, Pakistan from December 2022 to May 2023.
Methodology: After taking an informed consent from each study subject a total of 72 type 2 diabetic patients were enrolled in this study and all of them underwent thyroid tests, including TSH, free T3 and free T4. Seventy-two non-diabetic subjects of same age group were considered as controls .Diabetic status was assessed by fasting blood sugar, random blood sugar and HbA1c levels. Data was entered and analyzed using SPSS version 23.
Results: Out of 144 participants, 55.6% of the type 2 diabetic were male and 44.4% were female. The Mean age of the patients was 53.1 years. In type 2 diabetic patients, 61.1% were found with subclinical hypothyroidism, 1.4% were with subclinical hyperthyroidism and 37.5% were found normal while in controls TSH levels were normal.
Conclusion: Increase in TSH level was considered as another risk factor for the progression of type 2 diabetes in euthyroid subjects and there is high prevalence of subclinical hypothyroidism among type 2 diabetes patients compared to non-diabetic subjects.
Key words: Diabetes mellitus, hyperthyroidism, hypothyroidism, thyroid stimulating hormone.

Introduction

Diabetes Mellitus (DM) is metabolic disorder marked by sustained hyperglycemia due to defect in insulin secretion, its action or both. It is primarily classified into Type 1 and type 2 Diabetes mellitus (DM). Type 2 DM, a prevalent type of Diabetes, is largely associated with insulin resistance as identified by the international diabetes federation, reporting 4.2 million deaths and 463 million adults living with diabetes in 2019, with an expected increase by 2045 to 700 million.[1,2] The thyroid gland, an essential organ in human body stimulated by thyroid stimulating hormone (TSH) of the anterior pituitary gland, influencing the release of thyroid hormones that play a crucial role in regulating glucose metabolism.[3] Both T2DM and thyroid disorder are chronic endocrine diseases requiring lifelong management. Prevalence of thyroid disorder and diabetes mellitus varies in the general population, with thyroid disorder prevalence in type 2 DM ranging from 4-35%.[4] In Karachi, the prevalence of thyroid dysfunction is 36.9%, of which subclinical hypothyroidism accounts for 17.4%.[5] An increase in prevalence of thyroid disease is common in both type 1 and type 2 diabetes mellitus patients. Autoimmunity helps to explain the relation between Type 1 DM and autoimmune thyroid diseases; however, the link between T2DM and TD is more complex.[6] Previous studies reported that in type 2 diabetic patients there is an increase

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Authors Contribution

NA & SS conceptualized the project. NA, SAS & MSAJ did the data collection and literature search. MSAJ, SJ & SK performed the Statistical analysis. Drafting, revision & writing of manuscript were done by NA, SS, SJ & SK.

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prevalence of thyroid disorders compared to non-diabetic subjects, with obvious hypothyroidism often detected in type 2 diabetes mellitus.[7] Unidentified thyroid abnormalities can disrupt metabolic regulation in individuals with diabetes and potentially exacerbate pre-existing cardiovascular risks.[8]

Routine thyroid tests are not commonly performed in hospitals for type 2 diabetic patients, despite the high frequency of thyroid disease in this population. Thyroid hormone levels and Type 2 diabetes mellitus relation is highly challenging, and some studies have demonstrated contradictory results. Many studies have recommended confident results of high TSH levels and decrease FT4 and FT3 in hyperglycemia and insulin resistance, but some revealed no connection, that's why the aim of the study is to compare the levels of TSH in type 2 Diabetic patients and non-Diabetic subjects. It also aims to draw attention to the predictors of thyroid disorders in such patients and to examine the association of thyroid function with the diagnosed patient of type 2 diabetes.

In addition to monitoring glucose levels, holistic clinical management of type 2 Diabetes involves a focus on energy balance, where the evaluation of thyroid hormones levels may aid in addressing abnormalities and facilitate monitoring and assessment of new treatments that emphasizing energy expenditure.

Methodology

A prospective case control study was conducted from December 2022 to May 2023 on 144 subjects, with 72 diabetic patients and 72 non-diabetic individuals enrolled from National Medical Center Hospital, Karachi. After obtaining informed consent from the patients, study subjects were briefed about the study objectives. Subsequently, general health characteristics, medical examination and blood investigations were conducted using a subject evaluation form. All case subjects included in the study had Type 2 DM, duration of 2 years and were being treated with oral hypoglycemic agents, insulin, or a combination of both. The subjects underwent further examination, including blood pressure measurements recorded using a mercury sphygmomanometer calibrated for accuracy. Blood samples from both cases and controls were analyzed for fasting blood sugar (FBS), random blood sugar (RBS) and HbA1c levels was checked by using Roche 501 (Routine Chemistry Analyzer). Diabetic Patients above 40 years of age with fasting blood sugar of ≥126 mg/dL, HbA1c >6.5%, and RBS levels >200 mg/dL were registered in the study. History of type 1 diabetes mellitus patients, known thyroid dysfunction and patients with liver disease, renal disease, hypertension and pregnancy were excluded. Thyroid function test i.e., TSH was performed on both groups using the Chemiluminescence Abbott 1000 ISR (Immunoassay Analyzer). In type 2 Diabetics, subjects were labelled as hypothyroidism if TSH levels were measured high i.e., >4.5 IU/ml; subsequent FT3 and FT4 levels were normal. In controls, TSH levels were recorded as normal. According to National medical center lab, the reference normal range taken as: TSH: 0.4-4.5 IU/ml, T3: 2-4.4 pg/ml, FT4: 0.8-2.7 ng/dl. Thyroid disorders were classified as clinical hypothyroidism if TSH levels were > 4.5IU/ml and FT3 and FT4 levels were lower than 2 pg/ml and 0.8ng/dl. Subclinical hypothyroidism was diagnosed if TSH levels were >4.5 IU/ml and FT3 and FT4 levels were in normal range i.e., 2.4-4 pg/ml and 0.8-2.7 ng/dl, Subclinical hyperthyroidism was identified if TSH levels were lower than 0.4 IU/ml and FT3 and FT4 levels were in the normal range (2.4-4 pg/ml and 0.8-2.7 ng/dl). Clinical hyperthyroidism was diagnosed, if TSH levels were lower than 0.4 IU/ml and FT3 and FT4 were increased above 4 pg/ml and 2.7 ng/dl.

The data was analyzed and then stored by SPSS version 23. 0. Associations were assessed using the Pearson Chi-square test, revealing a correlation between age, gender, education, and diabetic status in both cases and controls. To compare the mean of these between cases and controls variable Independent sample t-test was used with p-value <0.05 considered as statistically significant.

The ethical approval was obtained from the Ethical Review Committee of Bahria University, Karachi vide letter no. 112/2022.

Results

Total 144 subjects were included, with 72 diagnosed patients of type 2 diabetes. Among the diabetic group 44.4% were female, with a mean age was 53.1(SD=±11.1) years and among 50% control group samples 69.4% were female, mean age was 49.1 (SD=±7.8) years, as indicated in Table-1. In type-2 diabetic patients' prevalence of thyroid dysfunction revealed that 61.1% had subclinical hypothyroidism, 1.4% had subclinical hyperthyroidism and 37.5% had normal thyroid function depicted in Figure-1. In the control group, the mean TSH was 2.3 (SD=±1.3) while in the cases mean TSH was 4.3 (SD=±2.9) Figure-2. An independent sample t-test indicated that the mean TSH of cases was significantly higher than that of controls (p <0.01) as shown in Table-2. Analyzing

Table 1: Baseline characteristics of studied samples. (n=144)

Characteristics		Group			
		Control (n=72)		Cases (n=72)	
		n	%	n	%
Gender	Male	22	30.6	40	55.6
	Female	50	69.4	32	44.4
	Mean (±SD)	49.1	7.8	53.1	11.1
Marital status	Single	1	1.4	2	2.8
	Married	71	98.6	68	94.4
	Widowed	-	-	2	2.8
Education	Primary	9	12.5	15	20.8
	Secondary	31	43.1	40	55.6
	Graduate	30	41.7	13	18.1
	Masters	2	2.8	4	5.6
Exercise	Exercise	15	20.8	26	36.1
	Don't Exercise	57	79.2	46	63.9
Family history of Diabetes	Yes	-	-	72	100
	No	72	100.0	-	-
Hypertension	No	72	100.0	72	100.0
Diabetes Duration >2-years	Yes	-	-	72	100.0
Oral Hypoglycemic	Yes	-	-	72	100.0

*p<0.05 was considered statistically significant

Table 2: Mean Comparison of TSH and Descriptive on FT3, FT4 for Cases.

Variables	Groups				p-value
	Controls		Cases		
	Mean	SD	Mean	SD	
TSH	2.3	1.3	4.3	2.9	<0.01*
FT3	-	-	3.0	0.7	N. A
FT4	-	-	1.4	0.4	N. A

*p<0.05 was considered statistically significant

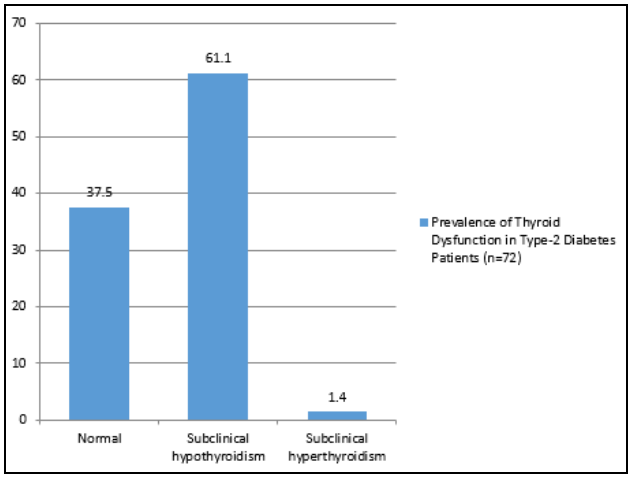

Figure 1: Prevalence of thyroid dysfunction in Type-2 diabetes patients. (n=72)

the thyroid dysfunction association with age, gender & other parameters, subclinical hypothyroidism was more common in aged ≤45 years among type 2 diabetic patients. Of these, 59.1% were male and 40.9% were female as shown in Table-3.

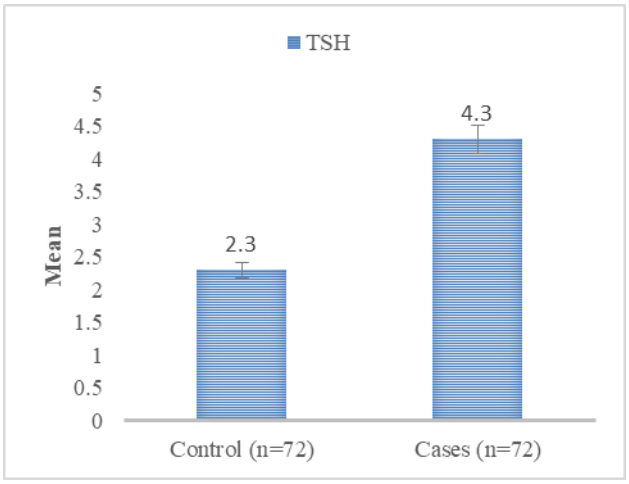

Figure 2: Mean comparison of TSH between cases and control

Discussion

In clinical practice, Thyroid disorder and Diabetes mellitus are the two most common endocrine disorders. Managing both conditions simultaneously is challenging particularly when there is co-existence of thyroid abnormality with diabetes.[5] Thyroid hormones itself plays a role in intermediary metabolism, leading to alteration in glucose homeostasis. Hypothyroidism induces a decrease in liver glucose output, gluconeogenesis and peripheral glucose utilization potentially resulting in hypoglycemia. Furthermore, in type 2 Diabetic patients, thyroid function can be influenced

Table 3: Association of thyroid dysfunction with Type 2 diabetes.

Variables		Thyroid Dysfunction						*p*-value
		Normal		Subclinical Hypothyroidism		Subclinical Hyperthyroidism		
		N	*%*	*N*	*%*	*N*	*%*	
Age Group	<45 years	10	37.0	13	29.5	0	0.0	0.72
	46 - 55 years	9	33.3	12	27.3	1	100.0	
	56 - 65 years	5	18.5	12	27.3	0	0.0	
	>65 years	3	11.1	7	15.9	0	0.0	
Gender	Male	14	51.9	26	59.1	0	0.0	0.44
	Female	13	48.1	18	40.9	1	100.0	
Marital status	Single	0	0.0	2	4.5	0	0.0	0.61
	Married	27	100.0	40	90.9	1	100.0	
	Widowed	0	0.0	2	4.5	0	0.0	
Education	Primary	7	25.9	7	15.9	1	100.0	0.40
	Secondary	15	55.6	25	56.8	0	0.0	
	Graduate	3	11.1	10	22.7	0	0.0	
	Masters	2	7.4	2	4.5	0	0.0	
Exercise	Exercise	12	44.4	14	31.8	0	0.0	0.42
	Don't Exercise	15	55.6	30	68.2	1	100.0	
Diabetes-2	Yes	26	96.3	42	95.5	1	100.0	0.96
	No	1	3.7	2	4.5	0	0.0	
Hypertension	Yes	0	0.0	0	0.0	0	0.0	N. A
	No	27	100.0	44	100.0	1	100.0	
Diabetes 2 Duration: (2 years)	Yes	27	100.0	44	100.0	1	100.0	N. A
	No	0	0.0	0	0.0	0	0.0	
Oral Hypoglycemics	Yes	27	100.0	44	100.0	1	100.0	N. A
	No	0	0.0	0	0.0	0	0.0	

*p<0.05 was considered statistically significant

by use of medications.[9] In current study, the mean age in the controls group was 49.1(SD±7.8 years) while in the cases, it was 53.1 (SD±11.1years), the findings of Nair and Ogbonna et al., align closely with those of our results.[10,11] Among the 72 T2DM individuals, 44.4% were female and 55.6% were male.[12-15]

To identify the thyroid irregularities, the levels of FT3, FT4 and TSH were evaluated in the present study, 27 out of 72 diabetic patients (37.5%) were classified as euthyroid, exhibiting normal levels of FT3, FT4, and TSH. Interestingly 62.5% (45 out of 72) of the diabetic patients showed thyroid abnormalities, with 59.1% were male. There was notably higher proportion of thyroid dysfunction in T2DM i.e., 62.5%, compared to non-diabetic individuals. Elevated TSH levels were also documented in various studies.[16]

Individuals with type 2 diabetes were assessed for presence of subclinical hypothyroidism, determined by elevated serum TSH levels while maintaining normal FT3 and FT4 levels in the cases, which was also indicated in prior studies.[17]

In prior studies where subclinical hypothyroidism was frequently observed in females and older aged groups, our study revealed a higher proportion of subclinical hypothyroidism in males and the younger population, specifically 29.5% in the age range of 35 to 45 years.[14,18]

The precise mechanism responsible for thyroid dysfunction in individuals with type 2 diabetes remains unclear. Some studies suggested that metabolic control may influence the hypothalamic -pituitary thyroid axis. Those with uncontrolled diabetes, the nocturnal TSH peak may be eliminated and the response of TSH to TRH stimulation might be blunted, potentially contributing to hypothyroidism development in type 2 diabetic patients.[8] In case of hypothyroidism the effect of hyperinsulinemia on thyroid gland is identified as a major factor which has been extensively documented in various studies between thyroid disease and diabetes disorders.[19] And also at the conversion of T4 to T3 in the peripheral tissue.[5]

Limitations included single centered study with small sample size, FT3 and FT4 not measured in controls as TSH levels were normal and presence

of financial constraints. In this study significant link between the glycemic status and levels of thyroid hormones was identified, high TSH level was a significant contributor for raised glycemic variability. It is the first study which showed subclinical hypothyroidism was not only common in female and older aged group but also common in males and younger population.

In euthyroidism type 2 DM; thyroid dysfunction prevalence was higher as compared to non-diabetic individual. Subclinical hypothyroidism was more prevalent and it was more common in males than females. Age over 40 years, family history of diabetes and gender (male) are the significant risk factors. Proper management & glycemic control can contribute to reducing the risk of thyroid disorder. Therefore, there is prerequisite for routine test of thyroid hormones in diabetic patients. It will help in the early detection, improving the management of overall reduction on morbidity and mortality in diabetic patients.

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Conflict of interest: None declared.

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