



Original Research Article

Evaluation of Thyroid Function Tests in Patients with Uncontrolled Type 2 Diabetes Mellitus

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ABSTRACT

Diabetes Mellitus and thyroid disorders are the most common endocrinal disorders seen in clinical practice. India has already become the “diabetes capital” of the world. The World Health Organisation estimate of diabetes prevalence for all age groups world-wide was 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. Occasionally, abnormal thyroid hormones levels are found in diabetes mellitus patients. The presence of undetected thyroid dysfunction may affect glycemic control in diabetics.

Aims:

1. To evaluate the thyroid functions tests of patients with uncontrolled type 2 diabetes mellitus (T2DM).
2. To assess the spectrum of the thyroid dysfunction in patients with uncontrolled T2DM and compare it with that of controlled T2DM patients.
3. To validate thyroid function screening of patients with uncontrolled T2DM.

Methods and Materials: After satisfying all the inclusion and exclusion criteria, 75 patients of T2DM with HbA1C levels > 7 were considered as uncontrolled T2DM patients and studied in the case group whereas 75 patients of T2DM with HbA1C levels < 7 were considered as controlled T2DM patients and studied in the control group.

Results:

1. The prevalence of thyroid dysfunction seen in the patients with uncontrolled T2DM was 53.33%.
2. Sub-clinical hyperthyroidism was the predominant underlying thyroid dysfunction pattern.
3. Prevalence of thyroid dysfunction in T2DM patients increases with age. Prevalence is higher if the patient has uncontrolled T2DM.
4. Prevalence of thyroid dysfunction was highest in patients more than 60 years of age.

Conclusions:

1. Greater the duration of uncontrolled T2DM in a patient, higher is the chance of thyroid dysfunction in him.
2. HbA1c can be used as a test to decide if screening for thyroid dysfunction is needed in T2DM patients or not.

Key words: Uncontrolled type 2 diabetes mellitus, Controlled type 2 diabetes mellitus, Thyroid function tests, Hypothyroidism, Hyperthyroidism.

Key Message:

Underlying hyperthyroidism should be considered in T2DM patients with unexplained worsening glycemic control followed by thyroid function screening for early detection and management.

INTRODUCTION

Diabetes mellitus (DM) is a group of aetiologically different metabolic defects characterized by hyperglycaemia resulting from a variable interaction of hereditary and environmental factors and is due to defect in insulin secretion as well as insulin action or both. [1] The influence of other endocrine and non-endocrine organs other than the pancreas on diabetes mellitus is documented. [2,3,4] The role of hyperthyroidism in diabetes was investigated in 1927, by Coller and Huggins proving the association of hyperthyroidism and worsening of diabetes. It was shown that surgical removal of parts of thyroid gland had an ameliorative effect on the restoration of glucose tolerance in hyperthyroid patients suffering from coexisting diabetes. [5] The first reports showing the association between diabetes and thyroid dysfunction were published in 1979. [6,7] Since then a number of studies have estimated the prevalence of thyroid dysfunction among diabetes patients to be varying from 2.2 to 17 %. [8,9] A plethora of studies have evidenced an array of complex intertwining biochemical, genetic, and hormonal malfunctions mirroring pathophysiological association between diabetes mellitus and thyroid dysfunction. [10,11] 5'adenosine monophosphate activated protein kinase is a common central target for modulation of insulin sensitivity and feedback of thyroid hormones associated with appetite and energy expenditure. [11] Autoimmunity has been implicated to be the major cause of thyroid-dysfunction associated diabetes mellitus. [12,13,14] Hyperthyroidism is typically associated with worsening glycemic control and increased insulin requirements. There is underlying increased hepatic glucone-

genesis, rapid gastrointestinal absorption of glucose and probably increased insulin resistance also. Indeed, thyrotoxicosis may unmask latent diabetes. Wide ranging changes in carbohydrate metabolism are seen in hypothyroidism, clinical manifestations of these abnormalities are seldom conspicuous. The reduced rate of insulin degradation in hypothyroidism may lower the exogenous insulin requirements. The occurrence of hypoglycemic states is uncommon in isolated thyroid hormone deficiency and should raise the doubt of hypopituitarism in a patient with hypothyroidism. [15,16]

The relation between DM and thyroid dysfunction may behold answers to various facts and therefore the present study was taken up in patients admitted at our tertiary care hospital.

MATERIALS AND METHODS

- **Study Design:** One year, prospective case-control study.
- **Working definition of Uncontrolled Type 2 Diabetes Mellitus.** [17]

Patients of type 2 diabetes mellitus with HbA1c levels more than 7.

- **Source of Data**

The study includes the DM patients admitted to medicine IPD of KIMS, Karad in the period between august 2012 to august 2013.

- **Inclusion criteria:**

- a. Known/old patients of T2DM.
- b. Newly detected patients of DM with FBS >126 mg/dl and PPBS >150 mg/dl that could be completely managed with OHA's. These patients were also considered as T2DM patients.

- c. Cases – T2DM patients with an HbA1c more than 7.
- d. Controls – T2DM patients with an HbA1c less than or equal to 7.
- **Exclusion criteria:**
 - a. T2DM patients with known thyroid disorders.
 - b. T2DM patients taking drugs like amiodarone or immunomodulators.
 - c. Severely ill T2DM patients with complications of diabetes mellitus.
- **Sample size:**
 - a. Number of cases: 75
 - b. Number of controls: 75
- **Investigations:**
 - a. Fasting blood sugar levels (FBSL)
 - b. Post-prandial blood sugar levels (PPBSL)
 - c. HbA1c
 - d. Serum Triiodothyronine (T3)
 - e. Serum Thyroxine (T4)
 - f. Serum Thyroid Stimulating Hormone (TSH)

Normal reference values:

FBS = 90-126 mg/dl
 PPBS = 100-150 mg/dl
 T3 = 52-185 ng/dl
 T4 = 4.6-10.7 microgram/dl
 TSH = 0.28-6.82 microIU/lit

Methods

Informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. All patients who met the inclusion and exclusion criteria were subjected to:

a. **Detailed History-**

Presenting illness, symptoms of diabetes and thyroid dysfunction, past history, duration of diabetes and on-going treatment at presentation.

b. **Physical Examination-**

To look for evidence of pre-existing thyroid dysfunction.

c. **Investigations-**

- Estimation of blood glucose was done by a method based on GOD/POD principle.
- HbA1c estimation was done by ion-resin method.
- T3, T4 and TSH estimation was done by an assay based on immuno-enzymometry.

Statistical analysis used:

Data was statistically analysed using Students Unpaired T-Test, Chi square test, One Way ANOVA test, Karl Pearsons Correlation, Spearman's Correlation and Mann-Whitney tests. Graphpad InStat version 3.06, Microsoft Excel and Word softwares were also used.

P < 0.05 was considered to be statistically significant.

RESULTS

Initially, the two study groups were age and sex matched. Then we compared the mean FBS, PPBS and HbA1c levels in the cases and controls (Table-1). Students Unpaired T Test was used. No significant difference was seen in the levels of FBS and PPBS but extremely significant difference between the mean HbA1c levels was seen. Hence, our use of HbA1c as the parameter to divide the study population into cases and controls was justified.

Then we wanted to know if there existed any correlation between levels of FBS, PPBS, HbA1c levels and Thyroid function parameters in cases and controls (Table-2). Karl Pearson's correlation coefficient was used. P values were > 0.05 for FBS and PPBS. Hence, no significant correlation was seen. Spearman rank correlation (nonparametric test) was used to correlate HbA1c and TSH of cases as many patients in the case group had TSH levels

which could not be detected by the immunoenzymometric assay. Their values were considered zero approximately. In cases, P values for HbA1c were < 0.005 for T3 and TSH; whereas < 0.05 for T4. Hence, very significant correlation was seen. As the level of HbA1c increases, glycemic control reduces and there occurs increase in T3 and T4 levels i.e. T3 and T4 are inversely correlated with control of blood sugar levels indicated by HbA1c. As glycemic control reduces, there occurs reduction in TSH levels i.e. TSH is directly correlated to control of blood sugar levels. Hence, HbA1c levels can be used as parameters to decide if screening for thyroid dysfunction is required in patients with uncontrolled T2DM or not. No significant correlation of HbA1c was seen in the control group as P values were > 0.05 . Hence, lower the levels of HbA1c, lesser are the chances of significant correlation with thyroid dysfunction.

We proceeded to compare the mean T3, T4 and TSH levels in the cases and controls (Table-3). Students unpaired t test with Welch correction was applied for comparing T3 and T4 in cases and controls. Mann-Whitney Test (non-parametric test) was applied to get the p value for TSH as many patients in the case group had TSH levels which could not be detected by the immunoenzymometric assay. Their values were considered zero approximately. Extremely Significant difference between mean T3, T4 and TSH levels of the two study groups is seen. There was high prevalence of abnormally deranged T3, T4 and TSH values in patients with uncontrolled T2DM as compared to those with controlled T2DM.

We now assessed the prevalence of thyroid dysfunction in the two study groups. 40(53.33%) cases had thyroid dysfunction as compared to 9 (12%) controls. Overall prevalence of thyroid dysfunction in the cases and controls was 32.67% (49/150).

Chi Square Test was used. P value = < 0.0001 . Hence, difference seen was very significant. This indicates that as the control of blood sugar levels of diabetic patients becomes poor, they get more prone to thyroid dysfunction. Spectrum of thyroid dysfunction consisted of sub-clinical hyperthyroidism seen in- 24(32%) cases and 7(9.33%) controls, hyperthyroidism in 14(18.67%) cases and 1(1.33%) controls, hypothyroidism in only 1(1.33%) case and sub-clinical hypothyroidism seen in 1(1.33%) case and 1(1.33%) control.

We studied the duration of T2DM in cases and controls. Mean duration of T2DM in cases was 57.53 months and 31.42 months in controls. Mann-Whitney test (nonparametric test) was used for statistical comparison. Duration of T2DM in newly detected T2DM patients was considered to be 1 month approximately. As the P value was 0.0067; the difference seen was very significant. Hence, greater the duration of T2DM in a patient, more is the likelihood of patients' sugars being uncontrolled and vice-versa.

Large numbers of newly detected T2DM patients (55/150) were included in the study. Hence we compared the thyroid dysfunction seen in them and the old patients of T2DM (Table-4). Chi Square Test was used. In cases, P value = 0.0034 indicated a very significant difference. Whereas in controls, P value = 0.7419 indicated no significant difference. Hence, if patients of DM are not diagnosed early, their blood sugars levels will remain elevated for long/unknown duration. Longer the time taken for the diagnosis, higher will be the blood sugar and HbA1c levels. Higher the HbA1c values in newly detected patients of DM at presentation, more are the chances of concomitant thyroid dysfunction being present and vice versa. Spectrum of thyroid dysfunction consisted of sub-clinical hyperthyroidism seen in 13(17.33%) newly

detected cases and 2(2.67%) newly detected controls, hyperthyroidism in 4(5.33%) newly detected cases and 1(1.33%) newly detected control, hypothyroidism in 1(1.33%) newly detected case and sub-clinical hypothyroidism was not seen.

In both the study groups maximum number of T2DM patients with thyroid dysfunction (Table-5) belonged to the age group of more than 60 years i.e. 19 out of 40 abnormal cases (47.50%) and 5 out of 9 abnormal controls (55.56%). To look if this variation of thyroid function with age was by chance or not, we applied the “ONE WAY ANOVA” test. As p value obtained was < 0.0001 for cases as well as controls, the variation seen was significantly greater than by chance. Thus, uncontrolled as well as controlled T2DM patients with age more than 60 years were seen to have high prevalence of thyroid dysfunction.

The percentage of thyroid dysfunction was greater in male T2DM patients 18.67% (28/150) than the female

14% (21/150) including both the two study groups. Sub-clinical hyperthyroidism was predominant in both sexes of cases as well as controls. Thus, we compared the thyroid dysfunction seen in the two sex groups of the T2DM patients. Chi Square Test was used. P value = 0.7900 was seen. Thus, the difference was not significant statistically.

Lastly, none of the T2DM patients in this study was receiving insulin alone. On presentation to our hospital 26(34.67%) cases and 9(12%) controls were being treated by both oral hypoglycemic agents (OHA) as well as insulin, 30(40%) cases and 33(44%) controls were being treated by OHA alone whereas 19(25.33%) cases and 33(44%) controls were not receiving any treatment at presentation to the hospital. This indicates that as the glycemic control of diabetic patients becomes poor, need for dual therapy increases. Also, insulin may play a role in the thyroid dysfunction seen in patients with uncontrolled T2DM receiving dual therapy.

Table-1: Comparison of Levels of FBS, PPBS, HbA1C in Cases and Controls:

Parameters	CASES(n=75)	CONTROLS(n=75)	Student's Unpaired 't' test value	'p' value	Significance
	Mean ± SD	Mean ± SD			
FBS	199.09±93.87	211.07±94.72	0.7776	0.4381	NOT significant
PPBS	213.29±82.13	240.61±93.11	1.906	0.0586	NOT significant
HbA1C	8.9±1.27	5.86±0.77	17.799	<0.0001	Extremely significant

Table-2: Correlation between FBS, PPBS, HbA1C Levels and Thyroid Function Parameters in cases and controls:

	Karl Pearson's correlation coefficient value (r)					
	CASES			Controls		
	T3	T4	TSH	T3	T4	TSH
FBS	0.02099	-0.04824	0.07701	-0.0999	-0.0278	0.07052
P value	0.8582	0.6811	0.5114	0.3935	0.8124	0.5477
PPBS	0.09645	0.02211	-0.01686	-0.2231	-0.1062	0.01095
P value	0.4104	0.8506	0.8858	0.0544	0.3647	0.9257
HbA1C	-0.3397	-0.2540	0.3328	-0.07606	-0.04985	0.1712
P value	0.0029	0.0279	0.0035	0.5166	0.6710	0.1420

Table-3 Comparison of Thyroid Functions Parameters in Cases and Controls:

Thyroid Functions Parameters	Cases (n=75)	Controls (n=75)	'p' value
	Mean ± SD	Mean ± SD	
T3	113.17±61.703	96±35.229	0.0385
T4	10.51±4.37	8.236±2.52	0.0002
TSH	1.842±7.54	2.0808±2.915	<0.0001

Table-4: Comparison of incidence of Thyroid Dysfunction in Newly Detected and Old patients of T2DM in Cases and controls

Thyroid Function	Cases (n=75)		Controls (n=75)	
	Newly Detected	Old	Newly Detected	Old
Abnormal	18 (81.82%)	22 (41.51%)	3 (9.09%)	06 (14.29%)
Normal	4 (18.18%)	31 (58.49%)	30 (90.91%)	36 (85.71%)
Total	22 (29.33%)	53 (70.67%)	33 (44%)	42 (56%)
P value	0.0034		0.7419	

Table-5: Thyroid dysfunction in different age groups of cases and controls.

Age - groups	Cases (n=75)		Controls (n=75)	
	Normal	Abnormal	Normal	Abnormal
20-40	01 (1.33%)	04 (5.33%)	05 (6.67%)	01 (1.33%)
41-60	16 (21.33%)	17(22.67%)	30(40%)	03 (4%)
>60	18 (24%)	19 (25.33%)	31 (41.33%)	05(6.67%)
Total	35 (46.67%)	40 (53.33%)	66 (88%)	09(12%)

DISCUSSION

Thyroid hormones:

In the present study and in Pajouhi et al study, [18] the difference in the mean T3 levels between cases and controls is extremely significant. The same was not observed in the Schroner Z et al, [19] Pasupathi P et al [20] and Udiong CEJ et al [21] studies which had studied diabetics and non-diabetics.

In the present study, the difference in the mean T4 levels between cases and controls was extremely significant. It was significant in the studies of Pasupathi et al [20] and Udiong CEJ et al. [21] Pajouhi et al study [18] and Schroner Z et al study [19] did not show the same significance.

In the present study, the difference in mean TSH values in the cases and controls was extremely significant. Among the uncontrolled T2DM patients investigated, 50.67% had low levels of TSH while 2.66% had high levels. In the controlled T2DM patients 10.67% had low and 1.33% had high TSH values. These findings show a high prevalence of abnormal TSH levels (low/high) in the DM population. This was also reported by Pasupathi et al. [20] In Pajouhi et al study, [18] Udiong et al study [21] and Schroner Z et al study, [19] the difference in mean TSH in the cases and controls was not significant. Our observations are also in agreement with the reports of Suzuki et al [22] and Smithson [9]

who in separate studies found altered thyroid hormone levels of different magnitudes in diabetic patients.

Prevalence of Thyroid Dysfunction:

In the present study, results showed an overall thyroid dysfunction prevalence of 32.67% (49/150). 53.33% were in the uncontrolled T2DM group and 12% in controlled T2DM group. Gonem et al study results confirm a higher prevalence of thyroid dysfunction (especially sub-clinical hyperthyroidism) in the diabetic population (40% in South Asians & Afro-Caribbean), compared to that reported in the general population. [23] Radaieh et al, [24] Bal B. S. et al, [25] and Lotz H et al [26] found a prevalence of 12.5%, 40.4% and 15% respectively. These factors might explain the high prevalence of hyperthyroidism in patients with uncontrolled T2DM in the present study.

Thyroid Dysfunction in the Newly Detected T2DM patients:

In the present study, 81.82% newly detected uncontrolled T2DM patients and 9.09% newly detected controlled T2DM patients had abnormal thyroid dysfunction. The percentage was high when compared to old patients of uncontrolled T2DM and low when compared to old patients of controlled T2DM. Sub-clinical hyperthyroidism was the predominant dysfunction. Thus, if patients of T2DM are not diagnosed early, their blood sugars levels will remain

elevated for long/unknown duration. Longer the time taken for the diagnosis, higher will be their blood sugar and HbA1c levels. Higher the HbA1c values in newly detected patients of DM at presentation, more are the chances of concomitant thyroid dysfunction being present. This presentation has not been studied in any previous studies.

Need for Routine Screening for Thyroid Dysfunction:

In the present study, we conclude that there is need for the routine assay of thyroid hormones in T2DM patients, particularly in those patients whose conditions are difficult to manage. Early detection and treatment must be initiated for better management. Patricia Wu suggested that screening for thyroid abnormalities in all diabetic patients will allow early treatment of subclinical thyroid dysfunction.^[16] A sensitive serum TSH assay is the screening test of choice. In T2DM patients, a TSH assay should be done at diagnosis and then repeated at least every 5 years. Pashupathi et al study has shown a high incidence of abnormal thyroid hormone levels among diabetic patients.^[20] Their findings demonstrate that detection of abnormal thyroid hormone levels in the early stage of diabetes will help patients improve their health and reduce their morbidity rate.

Age distribution:

In the present study, age matched individuals in cases and controls were studied. Other previous studies have not done so.^[19,20,27] In the present study, we found significant increase in the prevalence of thyroid dysfunction as the age increased. Prevalence of thyroid dysfunction was highest in T2DM patients more than 60 years of age in cases as well as controls. The NHANES III study a survey of 17,353 subjects representing the USA population also had similar results.^[28] Udiong et al also

found the incidence of thyroid dysfunction increasing with age of diabetics.^[21]

Sex distribution:

In the present study, sex matched individuals in cases and controls were studied. Percentage of thyroid dysfunction was more in male T2DM patients (18.67%) than the females (14%). But this difference was not statistically significant. Sub-clinical hyperthyroidism was predominant in both sexes in cases as well as controls. According to Udiong et al the incidence of hyperthyroidism was lower in females (8%) than in males (11%).^[21]

Duration of Diabetes:

In the present study, the mean duration of T2DM was 57.53 months in cases and 31.42 months in controls. Very significant difference between duration of T2DM in the cases and controls was seen. It suggests; greater the duration of T2DM in a patient, more is the likelihood of his blood sugars being uncontrolled and higher is the chance of thyroid dysfunction; vis-à-vis. This indicates the necessity of early detection and treatment of T2DM as well as thyroid dysfunction.

Fasting and Post prandial blood sugar:

In the present study, the FBS and PPBS levels did not correlate well with the prevalence of thyroid dysfunction.

Glycated Haemoglobin:

In the present study, there was significant difference between mean HbA1c levels of the cases and controls. There was a significant correlation of HbA1c with thyroid dysfunction seen in patients with uncontrolled T2DM. Hence, HbA1c can be used as a test to decide if screening for thyroid dysfunction is needed in T2DM patients or not. None of the earlier studies have referred to this aspect.

Method of treatment of DM:

In the present study, 34.67% uncontrolled T2DM patients required both OHA's as well as insulin whereas only 12%

well-controlled T2DM patients required both. The abnormal thyroid hormone levels may be the outcome of the various medications the diabetics were receiving. For example, it is known that insulin enhances the levels of free thyroxine while it suppresses the levels of T3 by inhibiting hepatic conversion of T4 to T3. On the other hand, some of the oral hypoglycemic agents such as the phenylthioureas are known to suppress the levels of FT4 and T4, while raising the levels of TSH. [29] Sulfonylureas like carbutamide have been associated with development of goitres in laboratory animals. [30] These factors may explain the findings of low or high thyroid stimulating hormone levels in diabetic subjects. The presence of both high and low levels of thyroid hormones in diabetics in this study may also be due to modified TRH synthesis/release and may depend on the glycemic status of the diabetics studied. Glycemic status is influenced by insulin, which is known to modulate TRH and TSH levels. [31] R. Satish et al concluded that there is inter-dependence between insulin and thyroid hormones for normal cellular metabolism so that diabetes mellitus and thyroid diseases can mutually influence the other disease process. [32] When diabetes occurs in euthyroid individuals, it results in altered thyroid function tests with no clinical dysfunction. When hyperthyroidism occurs in the setting of euglycemia, 2-3% of these individuals may become diabetic. Hyperthyroidism results in hyperglycemia while hypothyroidism increases the susceptibility to hypoglycemia in diabetic patients thereby complicating the diabetic management in these individuals. Failure to detect thyroid dysfunction in diabetes may be a primary cause of poor management often encountered in some treated diabetics.

CONCLUSIONS

1. Greater the duration of uncontrolled T2DM in a patient, higher is the chance of thyroid dysfunction in him.
2. HbA1c can be used as a test to decide if screening for thyroid dysfunction is needed in T2DM patients or not.

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