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Effect of thyroid hormones on Hyperglycaemia in patients with Type 2 diabetes mellitus

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Abstract:

Background: Insulin and thyroid hormones are both involved in cellular metabolism and excess or deficit of either of these hormones may result in the functional derangement of the other. Thyroid hormone action has long been recognized as an important determinant of glucose homeostasis. The present study was conducted to find out the correlation between hyperglycaemia and thyroid hormones in patients with T2DM.

Methods: Two hundred subjects with T2DM were enrolled in the study. This included 100 newly diagnosed T2DM cases and 100 patients who were already on follow-up at our hospital. In addition, 100 normal healthy controls were also taken for the study. All subjects were investigated for FPG, HbA1C, FT3, FT4 and TSH.

Results: Out of total 200 patients with T2DM, 161 cases had normal thyroid parameters (group 1), 25 cases had sub-clinical hypothyroidism (group 2), 10 patients were diagnosed with primary hypothyroidism (group 3) and 4 cases had primary hyperthyroidism (group 4). The mean FPG was elevated in group 1(152.5 ± 23.8) and group 4 (173.65 ± 59.3). Mean HbA1C was higher in patients with hyperthyroidism (8.1 ± 2.5). Subjects were further divided into three groups based on the diagnosis of T2DM as newly diagnosed T2DM cases, patients who were on long term follow- up of T2DM and controls. The FPG & HbA1C was significantly higher ($p < 0.001$) in both newly diagnosed T2DM patients & in those cases who were on long-term follow-up. Mean TSH was significantly elevated in long term follow-up patients with T2DM (7.68 ± 5.75, $p < 0.001$) and newly diagnosed T2DM cases (5.32 ± 1.54, $p<0.001$), when compared with controls (3.22 ±1.5, $p < 0.001$).

Conclusion: We conclude that biochemical screening for thyroid disease is essential in diabetic patients; predominantly in patients whose associated conditions are difficult to accomplish and the possible symptoms of thyroid disease being camouflaged by the diabetic state.

Introduction:

Diabetes mellitus (T2DM) and thyroid dysfunction (TD) are the two most common endocrine disorders.[1] Insulin and thyroid hormones are both involved in cellular metabolism and excess or deficit of either of these hormones may result in the functional derangement of the other. [2] As a consequence it may be possible for an individual to be affected by both thyroid disorder and diabetes simultaneously. It has been earlier suggested that hyperthyroidism was associated with poor prognosis of diabetes and thyroid hormone are an important determinant of glucose homeostasis [3]. Number of studies have estimated the prevalence of thyroid dysfunction among diabetes patients that varies from 17% to 46% and most common disorder being subclinical hypothyroidism. [4, 5] Poorly controlled diabetes (both Type 1 and Type 2), may induce a "Low T3 state" characterized by low serum total and free T3 levels, increase in reverse T3 (rT3) but near normal serum T4 and TSH concentrations. [6] Low serum T3 may be due to reduced peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) via 5'monodeiodination reaction.[7] Poorly controlled diabetes may also result in impaired TSH response to TRH or loss of normal nocturnal TSH peak.[8] Also, TSH responses and low T3 state may normalize with improvement in glycaemic status and failure to identify the imbalance of thyroid hormones in patients with T2DM may be a major cause of poor management and diagnosis of diabetic patients. [9] Therefore, it is important to analyse thyroid hormones in T2DM patients as routine investigation. Based on this, the present study was conducted to find out the correlation between hyperglycaemia and thyroid hormones inpatients with T2DM.

Subjects and Methods:

The study was conducted at a tertiary care hospital in Pune. Two hundred subjects with T2DM were enrolled for the present study, this included 100 (50 %) newly diagnosed T2DM cases and 100 (50%) patients who were already on follow-up at our hospital. In addition 100 normal healthy controls without any history of T2DM and/or hypothyroidism were also taken for the study. The diagnosis of newly detected type 2 DM was based on the American Diabetes Association criteria for T2DM [10].

Patients with known thyroid disorders, congestive cardiac failure, urinary tract infection, ketonuria, pregnant females and patients with diseases that may affect thyroid function and patients on medications that affect thyroid function, were excluded from the study.

Approval was obtained from the subjects by taking the informed consent. All work was performed according to the International Guidelines for Human Experimentation in Biomedical Research, as per Helsinki guidelines [11].

Criteria for classification of TD: [12, 13]

1. **Normal** – when FT3, FT4, and TSH were within the normal range.
2. **Primary hypothyroidism** – when TSH is more than 5.2 µIU/L and FT3, FT4, is less than the normal value.
3. **Primary hyperthyroidism** - when TSH is less than 0.2 µIU/L and FT4, FT3, is more than the normal values.
4. **Subclinical hypothyroidism** – when TSH is more than 5.2 µIU/L and FT3, FT4, is within the normal range.
5. **Subclinical hyperthyroidism –** when TSH is less than 0.2 µIU/L and FT3, FT4, are within the normal range.

Biochemistry and hormone profile:

Under all aseptic precautions fasting morning blood sample was collected in EDTA containing vacutainer (2ml) and plain vacutainer (5ml). The blood was allowed to clot for 30 minutes and was centrifuged at 3000 rpm for 10 minutes, serum was separated and analysed immediately on the same day for blood sugar and thyroid profile. Fasting blood sugar was estimated by Glucose oxidase method on auto analyser [14]. HbA1c was estimated by ion exchange resin [15]. FT3 and FT4 were estimated by using Chemi Lumination Immuno Assay (CLIA) and TSH was estimated using Ultra-Sensitive CLIA method.

Statistical analysis

The data entry was carried using Microsoft Office Excel worksheet and then exported to statistical software and analysed using appropriate statistical tests by SPSS 11.5. Mean ± standard deviation was calculated by applying chi-square and student t-test. Correlation was calculated using the formula of Pearson correlation coefficient between HbA1c, FBS, and thyroid profile. The obtained results were analysed and inferences were drawn from these. P value ≤0.05 were considered as statistically significant.

RESULTS

Among 200 patients with T2DM, 161 cases (80.5%) had normal thyroid parameters (Group 1), 25 (12.5%) cases had sub-clinical hypothyroidism (Group 2), 10 (5%) patients were diagnosed with primary hypothyroidism (group 3) and 4 (2%) cases had primary hyperthyroidism (group 4). The details are given in table 1.

Table: 1

Parameter	**Group 1 (n = 161)**	**Group2 (n = 25)**	**Group 3 (n = 10)**	**Group 4 (n = 4)**
FT3 1.5 – 4.2 pg/ ml	2.2 ± 0.69	2.1 ± 0.66	1.02 ± 0.41	2.9 ± 0.39
FT4 0.8 – 1.68 pg/ml	1.09 ± 0.24	1.2 ± 0.23	0.58 ± 0.16	1.79 ± 0.08
TSH 0.2-5.2 µ IU/ml	4.9 ± 4.92	14.15 ± 0.75	15.48 ± 3.89	0.17 ± 0.08
FPG 70- 110 mg/dl	152.5 ± 23.8	145.4 ± 20.4	146.3 ± 19.7	173.65 ± 59.3
HBA1c 4.2 – 6.2%	7.7 ± 0.98	7.7 ± 1.1	7.0 ± 0.78	8.1 ± 2.5
Mean age	46.54 ± 10.7	51.6 ± 10.7	49.2 ± 9.7	54.7 ± 8.0

The mean ± SD of FPG was elevated in group 1(152.5 ± 23.8) and group 4 (173.65 ± 59.3). Similarly mean ± SD of HbA1C (8.1 ± 2.5) was higher in patients with hyperthyroidism. We further divided our subjects into three groups based on the diagnosis of T2DM. These were Group 5 as newly diagnosed T2DM cases, Group 6 as patients who were on long term follow- up of T2DM and Group 7 as controls (i.e. normal glycaemic indices). The details of thyroid parameters in these groups is given in table 2.

Table 2: Mean Values of Biochemical parameters in Type 2 DM (Group 5 & 6) and Controls (Group 7)

Parameter	Group5 (n = 100) (A)	Group 6 (n = 100) (B)	Group 7 (n = 100) (C)	P value (AC)	P value (BC)
FPG 70- 110 mg/dl	163.67 ± 24.88	139.92 ± 17.08	89.11± 13.30	< 0.001	<0.001
HBA1C 4.2 – 6.2%	8.04 ± 1.16	7.41 ± 0.78	5.05 ± 0.74	<0.001	<0.001
FT3 1.5 – 4.2 pg/ ml	2.42 ± 0.78	2.01 ± 0.82	2.76 ± 1.05	<0.001	<0.001
FT4 0.8 – 1.68pg/ml	1.17 ± 0.26	1.02 ± 0.28	1.21 ± 0.31	0.324	<0.001
TSH 0.2-5.2 µ IU/ml	5.32 ± 1.54	7.68 ± 5.75	3.22 ±1.5	<0.001	<0.001

The FPG & HbA1C was significantly higher (p <0.001) in both group 5 (163.67 ± 24.88; 8.04 ± 1.16) & Group 6 (139.92 ± 17.08; 7.41 ± 0.78).

Mean ± SD values of TSH was significantly elevated in Group 6 (7.68 ± 5.75, p < 0.001) and Group 5 (5.32 ± 1.54, p<0.001), when compared with controls (3.22 ±1.5, p < 0.001). However mean FT4 levels were comparable between Group5 and Group 7 (1.17 ± 0.26 vs 1.21 ± 0.31; p = 0.324.)

The Pearson correlation of TSH with fasting blood glucose and HbA1c in four categories of thyroid dysfunction is given in table 3. Group 1 include T2DM patients with normal thyroid parameters, Group 2 include T2DM patients with sub-clinical hypothyroidism, Group 3 include T2DM patients with primary hypothyroidism and Group 4 include T2DM patients with primary hyperthyroidism. FBG had positive correlation with TSH in cases except in those with primary hyperthyroidism (r = - 0.79).

Table 3:

Parameter	Group 1		Group 2		Group 3		Group 4	
	r	***P* value**	**r**	***P* value**	**r**	***P* value**	**r**	***P* value**
Fasting blood glucose (mg/dl)	0.09	0.255	0.528	0.007	0.65	0.04	-0.79	0.21
HbA1c (%age)	0.011	0.88	0.41	0.04	0.62	0.05	0.86	0.14

Discussion

The thyroid hormones, are the regulatory hormones that affect the metabolic processes throughout the body and also play a vital role in the glucose homeostasis by controlling insulin secretion and affect the supply of glucose in the blood. [16] Reduced glucose absorption from gastrointestinal tract accompanied by prolonged peripheral glucose accumulation, gluconeogenesis, diminished hepatic glucose output and reduced disposal of glucose are hallmarks of hypothyroidism hence leading to hyperglycemic state [17] This is in contrast to the patients with hyperthyroidism where increased glucose output from liver is the pivotal reason for the induction of hyperinsulinemia, induction of glucose intolerance, and development of peripheral insulin resistance. Glucose tolerance in thyrotoxicosis is caused by elevated hepatic glucose output along with upregulated glycogenolysis. [3, 18]

In the present study, we found lower levels of FT3 (2.42 ± 0.78, 2.01 ± 0.82), FT4 (1.17 ± 0.26, 1.02 ± 0.28) and higher level of TSH in both diabetic group i.e. those who were newly diagnosed cases and those who were on follow up (Table 2). A similar study by Singh G et al., showed that patients with T2DM had abnormal thyroid hormone levels and the level of FT3 and FT4 were significantly lower while the levels of TSH were significantly higher in T2DM as compared to nondiabetics. [19] We found significantly low FT4 ($P < 0.001$) in patients with T2DM who were on long term follow-up, this is inconsistent with the study by Swamy RM et al., that showed the serum T4 level was low and TSH was high in their cases with T2DM [20]. This can be explained by the synergical behaviour of **t**hyroid hormones to insulin that affect the action of insulin indirectly. Hence it can be possible that hyperglycaemia somehow affects the secretion of thyroid hormones by modulating TSH secretion by hypothalamus-pituitary axis, thereby leading to higher prevalence of hypothyroidism in patients T2DM. We found a positive correlation between parameters of hyperglycemia (FBG & HbA1c) and TSH in patients with hypothyroidism is in accordance with the results observed by Vibha Uppal et al. [21] and Velija-Asimi et al. [22] Various reasons have been put forward to explain the dysglycemia caused in hypothyroidism. Thyroid hormones synergistically exert their metabolic actions with insulin by upregulating the expression of genes involved in glucose metabolism. Hence in hypothyroidism, elevated TSH lead to peripheral resistance thereby leading to increased blood glucose levels [23, 24].

In addition, elevated TSH leads to decreased metabolism and turn-over of glycated serum proteins, which leads to increased HbA1c levels. Also, free-radicals accumulate in the tissues and inhibit proteolysis, further worsening the hyperglycemic condition in these patients. [25, 26].

We found that mean FBG (173.65 ± 59.3) and HbA1c (8.1 ± 2.5) was elevated in our patients with hyperthyroidism. Similar results were reported by sumit et al. This can be due to the changes in carbohydrate metabolism by the effect of T3 in glycogenolysis and gluconeogenesis. [26]

Conclusion:

We conclude that biochemical screening for thyroid disease is justified in diabetic patients; predominantly in patients whose associated conditions are difficult to accomplish and the possible symptoms of thyroid disease being camouflaged by the diabetic state.

Ethical justification:

Informed and written consent [in language they best understood] was taken before collecting data and blood sample. Only those individuals, who volunteered to participate in the study, were selected and the data was kept confidential. The study did not impose any financial burden on the study subjects and the institute, therefore the study was ethically justified.

Conflict of Interests:

The author declares that he has no conflict of interests.

Author's contribution:

All authors were involved in the conceptualization of the study. SM and AP contributed to the data acquisition and interpretation. MRR, IS and AAB helped greatly in data analysis and interpretation. SI and IS drafted the manuscript. All authors have read and approved the submitted version of the manuscript.

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