DERANGEMENTS OF THYROID FUNCTION IN DIABETIC PATIENTS- A CROSS SECTIONAL STUDY
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ABSTRACT

BACKGROUND
Diabetes mellitus is an ever-increasing problem in developing countries, due to rapid alterations in lifestyle. A significant percentage of longstanding diabetic patients show abnormalities in thyroid function. The present study is an attempt to study thyroid derangements in patients of diabetes mellitus. Prevalence of thyroid dysfunction in known cases of diabetes mellitus have been investigated and compared with the findings of other investigators.

MATERIALS AND METHODS
50 cases were selected at random from amongst confirmed chronic cases of diabetes mellitus attending the outpatient department (OPD) of a tertiary care hospital. Side by side, another 50 control subjects were selected from patients attending the OPD who were non-diabetic and had no obvious features of thyroid disease. The glycated haemoglobin (HbA1c), free thyroxine (fT4) and thyroid stimulating hormone (TSH) levels were assayed in all the subjects and compared to study thyroid derangements in confirmed diabetics and control subjects.

RESULTS
The results show an increased level of thyroid disorders in diabetic patients with 54% of them being euthyroid, 30% being hypothyroid and 16% being hyperthyroid. On the other hand, among the non-diabetic controls, 84% were euthyroid, 12% hypothyroid and 04% hyperthyroid.

CONCLUSION
Chronic diabetes mellitus does seem to have a definite association with thyroid disorders, with increased blood glucose favouring hypo or hyperthyroidism in about half of diabetic patients. The causes of this synergy may work both ways with increased blood glucose and altered insulin and thyroid hormone levels interacting in complex ways to influence each other.

KEYWORDS
Diabetes mellitus, euthyroid, hypothyroid, hyperthyroid, glycated haemoglobin, free thyroxine, thyroid stimulating hormone.

Aims and Objectives
The present study which is a hospital based, cross sectional, case-control one, will be of considerable help to the participants and also to the lay public in general. Underlying thyroid disorders can have a major impact on glucose control & untreated thyroid malfunctioning can lead to potential harmful consequences; revelation of an undiagnosed thyroid dysfunction (if any) will not only provide important corrective inputs in devising appropriate management of diabetes but will also enable the health care provider to initiate early curative measures in restoring the normal thyroid status, even in the non-diabetics (included in the study to serve as ‘controls’).

Exploration of the relation between diabetes mellitus and thyroid disorders will enable us to know the current trends of association of both these disorders in this part of the country & also to formulate the protocol for thyroid screening in diabetic patients, which in turn will allow early management of subclinical thyroid dysfunction (if any), because it is already documented that thyroid dysfunction can adversely affect diabetes control & has the potential to negatively affect the patient outcomes.4,5

MATERIALS AND METHODS
The present study deals with the effect of hyperglycaemia on thyroid hormone profile in diabetic population & was carried out in the semi urban population of Malda (a city of West Bengal, lying within the eastern part of India) and neighbouring areas. The present study was carried out on a total of 100 subjects which included 50 test subjects and 50 controls. Of the test subjects 32 were male and 18 were female.

The test subjects were chosen at random from the Diabetic clinic of the General Outpatient department (OPD) of Malda Medical College & hospital, Malda, West Bengal. The controls were subjects attending the general OPD, who did not have any evidence of endocrine diseases with a normal blood glucose levels. The selected subjects were of the age group of 25 to 65 years, with a mean of 45 years. Study period was from September, 2017 to March, 2018. Prior informed consent was taken from all the study subjects. Approval (in prescribed format) from the concerned Institutional Ethics committee (IEC) was also obtained before conduction of this study.

The glycated haemoglobin percentage (HbA1C %) was simultaneously estimated in all cases and controls to provide an effective guideline for the control of diabetes mellitus. The glycated haemoglobin is a better marker of medium and long-term blood glucose levels than the fasting or post prandial plasma glucose levels. In the present study, HbA1C% was estimated with a commercial kit (KERAGEN Technologies Pvt. Ltd., Bengaluru) using cation exchange resins followed by colorimetric estimation against standards. Venous blood is mixed with lysing reagent for the preparation of haemolysate. Elimination of the Schiff’s base is achieved during haemolysis. The haemolysate is then mixed with a weakly binding cation-exchange resin. The non glycated haemoglobin binds to the resin leaving Glycated haemoglobin (GHb) free in the supernatant. The GHb percentage is determined by measuring the absorbance of GHb fraction and of the total Hb at 415nm (405-420 nm) and is expressed as a percentage of the total haemoglobin content.

The thyroid status of both test and control subjects was studied using values of free thyroxine (FT4) and thyroid stimulating hormone (TSH). The parameters were estimated using standard commercial enzyme linked immunosorbent assay (ELISA) kits (ELISCAN- kits manufactured by RFCL Limited, Uttarakhland). TSH levels are expressed in units of μIU/ml, while FT4 levels are measured in units of ng/dl.

Inclusion Criteria
For cases
Patients attending the clinic were confirmed diabetics, who previously had fasting plasma glucose levels of more than 125 mg% at least two occasions. All patients were receiving some form of treatment.

For controls
All of them had normal fasting plasma glucose levels (less than 100 mg% on at least two occasions) and had no history of diabetes mellitus or thyroid disease.

Exclusion Criteria
For Cases
Newly diagnosed diabetics with disease of less than 3 years duration.

For Controls
History of clinical findings or recognizable causes suggestive of thyroid dysfunction. None of them were suffering from any acute or chronic illnesses nor from any hepatic, renal or cardiac impairment.

All the subjects under study (cases & controls) were Indians residing in Malda district of the state West Bengal and surrounding areas – which constituted a semi urban population, i.e. subjects were of same race and from the same geographic location

RESULTS
The results obtained from the study are presented in Tables 1 & 2 and graphically in Figure 1.

The values of HbA1c according to the levels determined by the kit manufacturer were as follows –
Good glycemic control- HbA1C values of 8.0 to 9.0%
Fair glycemic control- HbA1C values of more than 9.0% to 10.0%
Poor glycemic control- HbA1C values of more than 10.0%

Thyroid Status –
According to the kit manufacturer standards, subjects grouped as having normal (euthyroid) levels of thyroid hormones had FT4 & TSH values within the range of 0.8 – 2.0 ng/dl & 0.39 – 6.16 μIU/ml, respectively.
Subjects classified as having raised levels of thyroid hormones had fT4 values > 2.0 ng/dl, or TSH values < 0.39 μIU/ml, or both.

Subjects classified as having low levels of thyroid hormones had fT4 values < 0.8 ng/dl or TSH values > 6.16 μIU/ml, or both.

DISCUSSION

The present study shows the effect of chronically increased blood glucose levels on thyroid function. Out of the 50 diabetic cases, 27(54%) were euthyroid, 15(30%) were hypothyroid and 08(16%) were hyperthyroid. Therefore, a little less than half the number of cases had a disorder of the thyroid gland. Again, out of the non-diabetic controls, 42(84%) were euthyroid, 06(12%) were hypothyroid and 08(16%) were hyperthyroid. This shows that about less than one fifth of the controls had a thyroid disorder.

The above results clearly show us the influence of diabetes mellitus in thyroid disorders. The mechanism of such an influence is subject to many theories. It is known that insulin is a key player in the control of intermediary metabolism. It organizes the use of fuels for either storage or oxidation. Through these activities, insulin has profound effects on protein, carbohydrate, lipid and mineral metabolism. Therefore, derangements in insulin signaling resulting from insulin deficiency or resistance have widespread and devastating effects on many organs and tissues including the thyroid gland. In addition to insulin’s effect on entry of glucose into cells, insulin also stimulates the uptake of amino acids, again contributing to its overall anabolic effect. When insulin levels are low, as in the fasting state, the balance is pushed toward intracellular protein degradation. This may be a likely explanation for some of the hypothyroid effects of diabetes mellitus.

Long standing diabetes affects many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. The risk of chronic complications (vascular & nonvascular) increases as a function of the duration of hyperglycemia. Four molecular mechanisms of glucose induced damage have been proposed to justify most of the long-term complications of DM - (i) increased polyol pathway flux, (ii) increased intracellular advanced glycation end product (AGE) formation, (iii) activation of protein kinase C, and (iv) increased hexosamine pathway flux. Some or all of these factors may be responsible for the gradual derangement of thyroid function.

Whatever be the cause, it is also seen that thyroid disease in turn has an adverse effect on diabetic control. Thyroid hormones are hyperglycemic in action. Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin dependent entry of glucose into cells and increased gluconeogenesis and glycoalyysis to generate free glucose.

So, it is not difficult to understand that there is interdependence between insulin and thyroid hormones for normal cellular metabolism, so that diabetes mellitus and thyroid diseases can mutually influence the other disease process.

CONCLUSION

The present study attempts to find the effects of sustained hyperglycaemia in a population of diabetic patients on thyroid function. Diabetes appears to alter thyroid gland function in about half of the patients in the study, with 30% of diabetics being hypothyroid and 16% being hyperthyroid. Various theories may be postulated for these phenomena based on the present work and the investigations of other authors. It must however be kept in mind that even in the non-diabetic control population, 16% subjects had altered

<table>
<thead>
<tr>
<th>Thyroid Status</th>
<th>Total Subjects (n=50)</th>
<th>Male (n=32) [No. (%)]</th>
<th>Female (n=18) [No. (%)]</th>
<th>Total Subjects (n=30)</th>
<th>Male (n=20) [No. (%)]</th>
<th>Female (n=20) [No. (%)]</th>
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<tbody>
<tr>
<td>Euthyroid</td>
<td>27 (54%)</td>
<td>20 (62.55)</td>
<td>07 (38.9)</td>
<td>42 (84%)</td>
<td>26 (86.6)</td>
<td>16 (52)</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>15 (30%)</td>
<td>06 (18.75)</td>
<td>09 (50)</td>
<td>06 (12%)</td>
<td>02 (6.7)</td>
<td>04 (20)</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>08 (16%)</td>
<td>06 (18.75)</td>
<td>02 (11.1)</td>
<td>02 (04%)</td>
<td>02 (6.7)</td>
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Table 1. Values of HbA1c, fT4 and TSH in Cases and Controls (Mean ± Standard Deviation)

<table>
<thead>
<tr>
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<th>Cases (Diabetic)</th>
<th>Controls (non-diabetic)</th>
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<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
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<tr>
<td>HbA1c (%)</td>
<td>9.02 ± 0.56</td>
<td>8.86 ± 0.55</td>
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<tr>
<td>fT4 (ng/dl)</td>
<td>1.55 ±0.71</td>
<td>1.62 ±0.71</td>
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<td>TSH (μIU/ml)</td>
<td>3.24 ± 3</td>
<td>4.64 ± 3.2</td>
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Table 2. Percentage Distribution of Thyroid Disorder in Cases and Controls

Figure 1. Distribution of Thyroid Derangements between Cases and Controls
thyroid function. This points out to us the importance of screening for both raised blood sugar and thyroid function on a larger scale and the requirement of further studies on much larger populations to probe further the relations between the functions of the pancreas and the thyroid glands.

REFERENCES