EVALUATION OF THYROID FUNCTION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS.

Biochemistry

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ABSTRACT

Introduction: Diabetes mellitus and thyroid disorders are the most common endocrine disorders seen in clinical practice. The presence of undetected thyroid dysfunction may affect glycemic control in diabetics. The current retrospective study was to evaluate thyroid function tests in patients with type 2 diabetes mellitus (T2DM).

Materials and Methods: In this retrospective study we included diabetic patients who performed thyroid function tests i.e. free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) and the thyroid dysfunction was stratified as hypothyroidism, subclinical hypothyroidism, hyperthyroidism, subclinical hyperthyroidism with reference to hormonal levels.

Results: Prevalence of thyroid dysfunction in T2DM patients increases with age. Prevalence is higher if the patient has uncontrolled T2DM. Hypothyroidism is present in 3.8% of diabetics and subclinical hypothyroidism is present in 18.8% of diabetics. Hyperthyroidism is present in 61% of diabetics and subclinical hyperthyroidism is present in 13.4% of diabetics. Of the diabetic groups 3% were euthyroid.

Conclusions: Greater the duration of uncontrolled T2DM in a patient, higher is the chance of thyroid dysfunction. Females and advanced aged patients are more vulnerable to thyroid dysfunction. These data reinforce that diabetes patients with thyroid comorbidity need more endocrine attention. HbA1c can be used as a test to decide if screening for thyroid dysfunction is needed in T2DM patients or not.

KEYWORDS

Diabetes, Hypothyroidism, Hyperthyroidism, FT3, FT4, TSH

This was a hospital based study conducted in the Department of Biochemistry, Sree Narayana Institute of Medical sciences, Ernakulam after getting ethical clearance from the hospital ethical committee. This retrospective study included diabetic patients who performed thyroid function tests i.e. free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) during the time period January 2013 to June 2015. Patients with incomplete thyroid function test were excluded from the study. The age and sex of the subjects were also noted.

In present retrospective study, a total of 385 diabetic patients were enrolled from January 2013 to June 2015. Among these patients 261 were female and 124 were male. 2.0 ml of venous blood was collected from the subjects in plain vial was allowed to clot and centrifuged at 3000 rpm for 15 minutes.

Thyroid function test panel (FT3, FT4 and TSH) were assayed by the ELFA (Enzyme linked fluorescent assay) method using Vidas kit. FT3 and FT4 were assayed by competitive immunnsmuass method with a final fluorescent detection and TSH was assayed by sandwich immunnsmuass method with a final fluorescent detection. All three parameters were estimated by following the same standard protocol provided by the manufacturer (VIDAS).

Estimation of blood glucose was done by a method based on GOD-POD principle. Glycated hemoglobin (HbA1c) estimation was done by Mannix C reagent (Nephelometry Agappe).

The reference interval for FT3, FT4 and TSH were 2.6–5.4 pg/ml, 6.9–12.6 pg/ml and 0.25–5.0 IU/ml respectively. Thyroid function is considered normal in euthyroidism when patients were presented with normal FT3, FT4 and TSH. Abnormal thyroid function was further categorized as hyperthyroidism (increased FT3, FT4 and decreased TSH), subclinical hyperthyroidism (increased FT3, FT4 and normal TSH), hyperthyroidism (decreased FT3, FT4 and increased TSH), and subclinical hypothyroidism (decreased FT3, FT4 and normal TSH).

Statistical analysis

Data was analyzed by Software Package for Social Sciences version 21 (SPSS 21). Data were represented as percentage, frequency, mean and standard error, students unpaired t test, Pearson’s correlation. Data were...
Results
In present retrospective study, a total of 385 subjects were enrolled from year January 2013 to June 2014. Among these subjects 261 were female and 124 were male. The subjects were classified according to thyroid status as hypo-thyroidism, hyperthyroidism, subclinical hypothyroidism, subclinical hyperthyroidism and euthyroidism taking reference of thyroid function test. Total hyperthyroidism includes hyperthyroidism plus subclinical hyperthyroidism and total hyperthyroidism represents hyperthyroidism and subclinical hyperthyroidism.

Of 195 T2DM patients, patients with HbA1c levels > 7 or FBS >126 mg/dl and PPBS >150 mg/dl were considered as uncontrolled T2DM patients and studied in the case group whereas 190 patients of T2DM with HbA1c levels < 7 or FBS <126 mg/dl and PPBS <150 mg/dl were considered as controlled T2DM patients and studied in the control group.

Table 1: Sex and age distribution of diabetic subjects.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>124</td>
<td>261</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>48.15± 5.13</td>
<td>46.05±4.99</td>
</tr>
</tbody>
</table>

Table 2: Comparison of Levels of FBS, PPBS, HbA1c in controlled & uncontrolled diabetic patients.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Uncontrolled diabetes (n=195) Mean ± SD</th>
<th>Controlled diabetes (n=190) Mean ± SD</th>
<th>Student's Unpaired t test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS</td>
<td>189.09±53.87</td>
<td>99.7± ± 34.72</td>
<td>14.381</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPBS</td>
<td>240.6±69.31</td>
<td>133.29±42.13</td>
<td>17.806</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.4±1.31</td>
<td>5.6±0.79</td>
<td>19.679</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3: Correlation between FBS, PPBS, HbA1c Levels and Thyroid Function Parameters in uncontrolled and controlled diabetes.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Uncontrolled diabetes</th>
<th>Controlled diabetes</th>
<th>Pearson’s correlation coefficient value (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS</td>
<td>0.921</td>
<td>0.392</td>
<td>0.8017</td>
</tr>
<tr>
<td>PPBS</td>
<td>0.806</td>
<td>0.424</td>
<td>0.858</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.518</td>
<td>0.243</td>
<td>0.862</td>
</tr>
<tr>
<td>p value</td>
<td>0.002</td>
<td>0.002</td>
<td>0.312</td>
</tr>
</tbody>
</table>

Table 4: Comparison of Thyroid Functions Parameters in uncontrolled & uncontrolled diabetes.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Uncontrolled diabetes</th>
<th>Controlled diabetes</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>5.5±2.2</td>
<td>3.8±2.3</td>
<td>0.03</td>
</tr>
<tr>
<td>T4</td>
<td>12.51±3.37</td>
<td>9.26±2.62</td>
<td>0.0002</td>
</tr>
<tr>
<td>TSH</td>
<td>1.68±0.64</td>
<td>2.10±0.31</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Fig 1: The distribution of thyroid disorder in type 2 diabetes mellitus.

Endogenous production of glucose is also enhanced in hyperthyroidism via several mechanisms. Thyroid hormones produce an increase in the hepatocyte plasma membrane concentrations of glucose transporter(GLUT2) which is the main glucose transporter in the liver and consequently the increased levels of GLUT2 contribute to the increased hepatic glucose output and abnormal glucose metabolism [17,18]. Additionally increased lipolysis is observed in hyperthyroidism resulting in an increase in free fatty acids (FFA) that stimulates hepatic gluconeogenesis. The increased release of FFA could partially be explained by an enhanced catecholamine-stimulated lipolysis induced by the excess thyroid hormones [19]. Moreover, the non-oxidative glucose disposal in hyperthyroidism is enhanced resulting in an overproduction of lactate that enters the Cori cycle and promotes further hepatic gluconeogenesis. The increase in growth hormone, glucagon and catecholamine levels associated with hyperthyroidism further contributes to the impaired glucose tolerance [20-22].

It is well known that diabetic patients with hyperthyroidism experience worsening of their glycemic control and thyrotoxicosis has been shown to precipitate diabetic ketoadidosis [21,24]. Chronic hyperglycemia from any route of cause leads to dyslipidemia alleviated thyroid stimulating hormone, cardiovascular diseases, renal diseases, neurological problems and recurrent infections.

The present study reveals different grades of thyroid dysfunction among diabetes. Hypothyroidism is present 3.8% of diabetics and subclinical hypothyroidism is present in 18.8% of diabetics. Hyperthyroidism is present in 61 % of diabetics and subclinical hyperthyroidism is present in 13.4 % of diabetics. If the diabetics groups 3% were euthyroid. This goes in accordance with the reports of Suzuki et al[6] and Smithson et al[25] who found altered thyroid hormone level of different magnitude (both low and high) in diabetic patient. The abnormal thyroid hormone level may be the because of various medications the diabetics was receiving. For example, it is known that insulin anabolic hormone enhances the level of FT4 while it suppresses the level of T3 by inhibiting hepatic conversion of T4 to T3 [28]. On the other hand some of the oral hypoglycemic agents such as the phenylthioureas are known to suppress the level of FT4 and T4, while causing raised levels of TSH [27,28]. Some of the type 2 diabetics were on oral hypoglycemic agents alone and some were on both insulin injections and oral hypoglycemic agents. These situations...
may explain the finding of low or raised thyroid hormone levels in some of the euthyroid diabetics. The presence of both raised and low levels of thyroid hormone levels in diabetics in this study may also be related to modified thyroid releasing hormone (TRH) synthesis and release. Major disturbances in the glucocorticoid status of the diabetics studied [29]. Glucocorticoids are influenced by insulin, which is known to modulate TRH and TSH levels [30].

The thyroid hormones, triiodothyronine and tetraiodothyronine are insulin antagonists that potentiate the action of insulin indirectly by TRH synthesis which decreases in diabetes mellitus. These facts could be responsible for the occurrences of low thyroid hormone levels in some diabetics.

The diagnosis of thyroid dysfunction in diabetic patients based solely on clinical manifestations can be difficult. Poor glycemic control can produce features similar to hyperthyroidism, such as weight loss despite increased appetite and fatigue. On the other hand, severe diabetic nephropathy can be mistaken for hypothyroidism because patients with this condition may have edema, fatigue, pallor, and weight gain.

To further complicate the diagnostic process, poorly controlled diabetes, with or without its complications, may produce changes in thyroid function both that occur in non-diabetic illnesses. Typical changes include a low serum T3 due to impaired extrathyroidal T4 to T3 conversion, a low serum T4 due to decreased protein binding, and an inappropriately low serum TSH concentration.

However, the underlying thyroid dysfunction can produce clinically important physiological effects. Subclinical hyperthyroidism can elevate serum LDL-cholesterol and worsen pre-existing dyslipidemia, further increasing the risk of atherosclerosis. Subclinical hyperthyroidism may increase the risk of cardiac arrhythmias and exacerbate angina. Since diabetic patients are at high risk for cardiovascular diseases, the diagnosis and treatment of subclinical thyroid diseases is important.

Therefore, it seems prudent to consider thyroid function in newly diagnosed as well as chronic diabetic patients. Thyroid dysfunction is common in diabetic patients and can produce significant metabolic disturbances. Therefore, regular screening for thyroid abnormalities in all diabetic patients will allow early treatment of subclinical thyroid dysfunction. This raises the issue whether routine screening for thyroid disease in all patients newly diagnosed with diabetes mellitus will be cost effective.

Conclusion
This study show high incidence of abnormal thyroid hormone level among type 2 diabetic subjects. Thyroid dysfunction is common in diabetic patients and can produce significant metabolic disturbances. Therefore, regular screening for thyroid abnormalities in all diabetic patients will allow early treatment of subclinical thyroid dysfunction. Females and advanced aged patients are more vulnerable to thyroid dysfunction. These data reinforce that diabetes patients with thyroid comorbidity need more endocrine attention. HbA1c can be used as a test to decide if screening for thyroid dysfunction is needed in TIDM patients or not. Due to the retrospective design, the limited number of patients and the high percentage of missing data in some patient groups our results need to be interpreted with caution. Further studies are needed to confirm our findings and elucidate mechanisms of interaction of thyroid disease in type 2 diabetes patients.

References