

## Effect of Glycaemic Control on Thyroid Hormones Level in Type 2 Diabetic Patients

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### Abstract

**Background:** Thyroid dysfunction, a common endocrine disorder that increasing day by day. Hypothyroidism occasionally occurs in diabetic patients especially those with poor glycaemic control.

**Objectives:** The objective of the study was to observe the effect of glycaemic control on thyroid hormones level in type 2 diabetic patients and to determine selected socio-demographic characteristics of the respondents.

**Methods:** This case control study was carried out in the Department of Physiology, Sir Salimullah Medical College (SSMC), Dhaka from July 2016 to June 2017. A total of sixty subjects of both male and female, age ranged from 40 to 60 years were included in this study. Among them, thirty were type 2 diabetic patients (both uncontrolled and controlled) and another thirty were included for comparison as control and were matched by age, sex, and body mass index (BMI). Both case and control group were selected purposively based on selection criteria. Serum TSH, FT<sub>4</sub> and FT<sub>3</sub> levels were measured by chemiluminescent micro particle immunoassay (CMIA) method. Fasting blood glucose level was estimated by glucose oxidase (GOD) method and blood HbA<sub>1c</sub> level was estimated by ion exchange high performance liquid chromatography (HPLC) method. The statistical analysis was done by ANOVA test, Bonferroni test and Pearson's correlation coefficient test. Quality control of data was maintained by using a checklist.

**Results:** In this study, mean serum TSH level was significantly higher in uncontrolled diabetic patients than that of controlled diabetic patients. Serum FT<sub>4</sub> level was significantly lower in uncontrolled diabetic patients in comparison to that of controlled diabetic patients. Besides these, serum TSH level was positively correlated ( $r = +0.575$ ), serum FT<sub>4</sub> and FT<sub>3</sub> levels were negatively correlated ( $r = -0.588$ ,  $r = -0.527$ ) with HbA<sub>1c</sub> level in uncontrolled diabetic patients and all these relationships were statistically significant  $p \leq 0.05$  respectively.

**Conclusion:** The present study revealed that hypothyroidism occurs in type 2 diabetic patients which were found only in uncontrolled diabetic patients due to their poor glycaemic control.

**Keywords:** Thyroid stimulating hormone, Free thyroxine, Free triiodothyronine, Glycaemic control.

### Introduction

Diabetes is characterized by chronic hyperglycemia associated with disturbances in protein and lipid metabolism on account of absolute or relative deficiency or inefficiency of insulin.<sup>1</sup> The reduced sensitivity to insulin is often called insulin resistance.<sup>2</sup> The prevalence of diabetes mellitus is increasing throughout the world due to population growth, aging, urbanization, increase prevalence of obesity and physical inactivity and increased consumption of refined foods globally.<sup>3,4</sup> Long term diabetes mellitus is associated with vascular complications like retinopathy, nephropathy, peripheral and autonomic neuropathy,

cardiovascular and cerebrovascular diseases but adequate glycaemic control can delay development of diabetic complication.<sup>5,6</sup>

Thyroid dysfunction is another common endocrine disorder that is also increasing day by day and manifests either as hyper or hypothyroidism that may occur in type 2 diabetic patients.<sup>7,8</sup> There is great variability in the prevalence of thyroid dysfunction in general population ranging from 6.6% to 13.4% where as in diabetic patients the prevalence is greater and varies from 10 to 24.0%.<sup>9</sup> This difference can be explained by different diagnostic criteria of thyroid disease, the degree of iodine intake among different regions, different sensitivities of the TSH assays and the large population diversity.<sup>10</sup> However, in type 2 diabetic patients

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hypothyroidism is more common than hyperthyroidism.<sup>11</sup> Some researchers observed that 28.8% of diabetic patients having abnormal thyroid hormone levels, 22.5% had hypothyroidism and 6.3% had hyperthyroidism.<sup>12</sup> In this country, another researcher found 16.3% thyroid dysfunction among type 2 diabetic patients (9.0% had hypothyroidism and 7.0% had hyperthyroidism).<sup>13</sup> Diabetes mellitus influence thyroid function mainly at two sites; first at the level of hypothalamic control of thyroid stimulating hormone release and second, at the conversion of  $T_4$  to  $T_3$ ,<sup>14</sup> especially those with poor glycaemic control.<sup>14,15</sup> Bartalena et al found that poor glycaemic control affects the hypothalamo-pituitary-thyroid axis.<sup>16</sup> It causes impairment of nocturnal TSH secretion, thyroid hormone secretion and their response to TRH stimulation.<sup>17</sup> On the other hand, higher circulating level of insulin associated with insulin resistance causes proliferation of thyroid tissue and formation of thyroid nodules.<sup>18</sup> Moreover, alteration of the secretory activities of thyroid gland causes low thyroid hormone level.<sup>19</sup> Uncontrolled diabetes is also associated with low serum  $T_3$  state and impaired production of  $T_3$  from  $T_4$ . Because the activity of thiol dependent hepatic enzyme  $T_4$ -5 deiodinase that causes peripheral conversion of thyroxin to triiodothyronine via 5 monodeiodination reaction is reduced.<sup>20</sup> Besides these, Sahu et al reported that thyroid peroxidase antibody is responsible for thyroid dysfunction in type 2 diabetic patients.<sup>21</sup>

The relationship between thyroid disorders and type 2 diabetes mellitus is characterized by a complex interdependent interaction. The prevalence of thyroid disorders in type 2 diabetic patients which is further found to be more in uncontrolled diabetic patients.<sup>22</sup> Some researchers suggested that, type 2 diabetic patients should measure serum TSH level yearly to detect asymptomatic thyroid dysfunction as it may help to achieve good glycaemic control.<sup>23,24</sup> Otherwise, it can aggravate classical risk factors such as dyslipidaemia and lead to an increased risk of cardiovascular events and nephropathy in these patients.<sup>6,25</sup>

## Materials and Methods

This case control study was conducted among 30 diagnosed type 2 diabetic patients age ranged from 40 to 60 years were selected from the Out Patient Department of Endocrinology, Sir Salimullah Medical College (SSMC) and

Mitford Hospital, Dhaka. The patients were diagnosed according to American Diabetic Association (ADA) criteria. Thirty apparently healthy subjects with similar age, BMI and socioeconomic status were selected as comparison/Control (Group A). Study group was again subdivided into two groups. Group B<sub>1</sub> included 17 uncontrolled diabetic patients and Group B<sub>2</sub> included 13 controlled diabetic patients. Both control and study groups were selected purposively. The study protocol was approved by Institutional Ethics Committee of SSMC. Diabetic patients with renal disease, known thyroid abnormalities, any other endocrine abnormalities and pregnancy were excluded from this study. After selection, the subjects were thoroughly informed about the aim, objectives and procedure of the study and were encouraged for voluntary participation. An informed written consent was taken from each subject. Data were generated using a standard pre-tested questionnaire. It was filled up by the principal investigator individually. In addition, samples were collected by the principal investigator as well. With all aseptic precautions 7 ml of venous blood was drawn by sterile disposable syringe from ante-cubital vein. Then 2 ml of whole blood was transferred to an EDTA tube for determination of HbA<sub>1c</sub> level. The remaining blood was transferred to a clean and dry glass test tube and was kept in slanted position till formation of clot. After centrifugation, supernatant serum was collected in labeled eppendorf test-tube and was used for different biochemical tests. In assessing thyroid function, serum TSH, FT<sub>4</sub> and FT<sub>3</sub> levels were measured by chemiluminescent microparticle immunoassay (CMIA) method in the Department of Biochemistry, BSMMU, Dhaka however, fasting plasma glucose level was estimated by glucose oxidase (GOD) method in the Department of Physiology, SSMC and HbA<sub>1c</sub> levels were estimated by ion exchange high performance liquid chromatography (HPLC) method in the Department of Biochemistry, BSMMU to observe participants glycaemic status. Correlation of HbA<sub>1c</sub> with serum TSH, FT<sub>4</sub> and FT<sub>3</sub> were done to observe its relationship. The data quality control was done using appropriate checklist. The statistical analysis was done by ANOVA test, Bonferroni test and Pearson's correlation coefficient test by using Statistical Package of Social Science (SPSS) windows. The ethical clearance was obtained from the Institutional Review Board of the Sir Salimullah Medical College (SSMC), Dhaka.

## Results

In this study, the mean fasting blood glucose level was significantly ( $p<0.001$ ,  $p\leq 0.05$ ) higher in uncontrolled and controlled diabetic patients in comparison to that of non-diabetic subjects and it was also significantly ( $p<0.001$ ) higher in uncontrolled diabetic patients in comparison to that of controlled diabetic patients. Again, the mean HbA<sub>1c</sub> level was significantly ( $p<0.001$ ,  $p<0.01$ ) higher in uncontrolled and controlled diabetic patients in comparison to that of non-diabetic subjects and it was also significantly ( $p<0.001$ ) higher in uncontrolled diabetic patients than that of controlled diabetic patients (table II).

**Table I:** Age, body weight & BMI in both groups (n=60)

| Groups | n  | Age (Year)              | Body weight (Kg)        | BMI (kg/m <sup>2</sup> )      |
|--------|----|-------------------------|-------------------------|-------------------------------|
| A      | 30 | 49.17 ± 7.02<br>(40-60) | 55.53 ± 6.32<br>(46-70) | 21.73 ± 1.56<br>(18.89-23.81) |
| B      | 30 | 51.43 ± 6.07<br>(40-60) | 55.87 ± 6.46<br>(50-70) | 23.15 ± 1.01<br>(20.57-24.44) |

Group A: Comparison group (Healthy non-diabetic subjects)

Group B: Study group (Diabetic patients)

n = Total number of subjects

**Table II:** Fasting blood glucose and HbA<sub>1c</sub> levels in different groups (n=60)

| Groups         | n  | Fasting blood glucose mmol/L | HbA <sub>1c</sub> % |
|----------------|----|------------------------------|---------------------|
| A              | 30 | 5.08 ± 0.64                  | 5.04 ± 0.42         |
| B <sub>1</sub> | 17 | 8.53 ± 1.16                  | 7.17 ± 0.63         |
| B <sub>2</sub> | 13 | 5.65 ± 1.08                  | 5.62 ± 0.51         |

Statistical analysis

| Groups                                | Fasting blood glucose | HbA <sub>1c</sub> |
|---------------------------------------|-----------------------|-------------------|
| A vs B <sub>1</sub> vs B <sub>2</sub> | <0.001***             | <0.001***         |
| A vs B <sub>1</sub>                   | <0.001***             | <0.001***         |
| A vs B <sub>2</sub>                   | 0.048*                | <0.003**          |
| B <sub>1</sub> vs B <sub>2</sub>      | <0.001***             | <0.001***         |

Group A: Comparison group (Healthy non-diabetic subjects)

Group B<sub>1</sub>: Uncontrolled diabetic patients

Group B<sub>2</sub>: Controlled diabetic patients

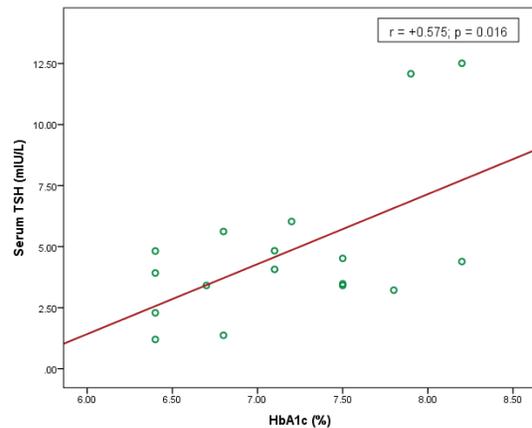
\*\*\* = Significant at  $p<0.001$ , \*\* = Significant at  $p<0.01$ ,

\* = Significant at  $p\leq 0.05$

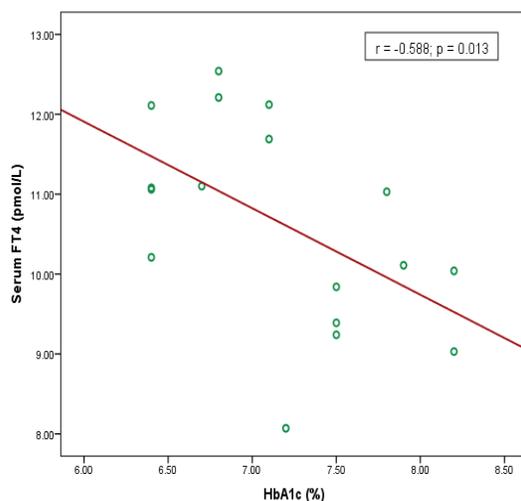
n = Total number of subjects

In this study, the mean serum TSH level was significantly ( $p<0.001$ ,  $p\leq 0.05$ ) higher in uncontrolled and controlled diabetic patients than that of non-diabetic subjects and it was also significantly ( $p<0.01$ ) higher in uncontrolled diabetic patients as compared to controlled diabetic patients. On the other hand, the mean

serum FT<sub>4</sub> level was significantly ( $p<0.01$ ,  $p\leq 0.05$ ) lower in uncontrolled diabetic patients than that of non-diabetic subjects and controlled diabetic patients. This level was lower in controlled diabetic patients than that of non-diabetic subjects but the difference was not statistically significant. However, the mean serum FT<sub>3</sub> level was significantly ( $p\leq 0.05$ ) lower in uncontrolled diabetic patients in comparison to that of non-diabetic subjects. FT<sub>3</sub> level was lower in controlled diabetic patients than that of non-diabetic subjects but the difference was not statistically significant. Again, this level was lower in uncontrolled diabetic patients than that of controlled diabetic patients but the difference was not statistically significant (table III). Moreover, HbA<sub>1c</sub> found positively correlated with serum TSH level and negatively correlated with serum FT<sub>4</sub> & FT<sub>3</sub> level (figure 1, 2, & 3).



**Figure 1:** Correlation of HbA<sub>1c</sub> with serum TSH in uncontrolled diabetic patients



**Figure 2:** Correlation of HbA<sub>1c</sub> with serum FT<sub>4</sub> in uncontrolled diabetic patients

**Table III:** Serum TSH, FT<sub>4</sub> and FT<sub>3</sub> levels in different groups (n=60)

| Groups         | n  | TSH<br>(mIU/L) | FT <sub>4</sub><br>(pmol/L) | FT <sub>3</sub><br>(pmol/L) |
|----------------|----|----------------|-----------------------------|-----------------------------|
| A              | 30 | 1.53 ± 0.77    | 13.29 ± 3.06                | 4.18 ± 0.82                 |
| B <sub>1</sub> | 17 | 4.77 ± 3.12    | 10.64 ± 1.29                | 3.66 ± 0.78                 |
| B <sub>2</sub> | 13 | 2.52 ± 1.46    | 12.21 ± 2.21                | 3.74 ± 0.80                 |

## Statistical analysis

| Groups                                | TSH       | FT <sub>4</sub>     | FT <sub>3</sub>     |
|---------------------------------------|-----------|---------------------|---------------------|
| A vs B <sub>1</sub> vs B <sub>2</sub> | <0.001*** | 0.004**             | 0.069 <sup>ns</sup> |
| A vs B <sub>1</sub>                   | <0.001*** | 0.003**             | 0.047*              |
| A vs B <sub>2</sub>                   | 0.046*    | 0.590 <sup>ns</sup> | 0.313 <sup>ns</sup> |
| B <sub>1</sub> vs B <sub>2</sub>      | 0.005**   | 0.041*              | 1.000 <sup>ns</sup> |

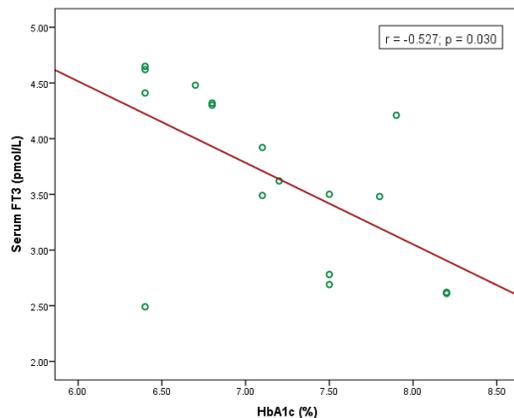
Group A: Comparison group (Healthy non-diabetic subjects)

Group B<sub>1</sub>: Uncontrolled Diabetic patientsGroup B<sub>2</sub>: Controlled Diabetic patients

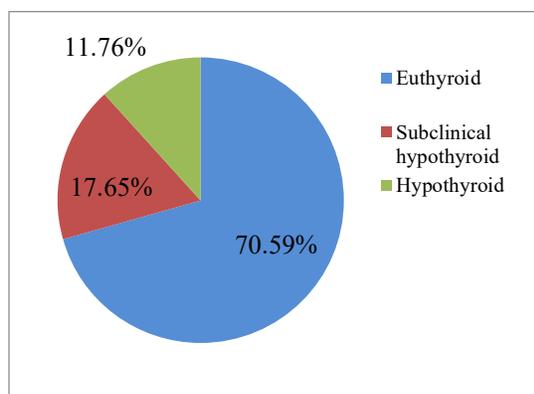
\*\*\*= Significant at p&lt;0.001, \*\*= Significant at p&lt;0.01, \*=

Significant at p≤ 0.05

ns = not significant n= total number of subjects

**Figure 3:** Correlation of HbA<sub>1c</sub> with serum FT<sub>3</sub> in uncontrolled diabetic patients

Again, in this study, among the uncontrolled diabetic patients, 70.6% were euthyroid, 11.8% were hypothyroid and 17.7% were subclinical hypothyroid (figure 4).

**Figure 4:** Distribution of thyroid dysfunction in uncontrolled diabetic patients (n=17)**Discussion**

This study observed thyroid function status in uncontrolled and controlled type 2 diabetic patients by measuring thyroid hormone levels. HbA<sub>1c</sub> level was also estimated to find out its level on diabetic patients and to correlate them with serum TSH, FT<sub>4</sub> and FT<sub>3</sub> levels. Results of this study showed serum TSH level was significantly higher in uncontrolled diabetic patients than that of controlled diabetic patients. This result agrees to other researchers.<sup>17</sup> The exact mechanism that was involved in high TSH level in type 2 diabetic patients was not yet clearly established. However, several investigators of different countries proposed various suggestions on this aspect. Some researchers reported that metabolic control affects the hypothalamo-pituitary-thyroid (HPT) axis and metabolic de-compensation leads to impairment of TSH secretion and TSH response to TRH stimulation was blunted in poorly controlled diabetic patients that cause hypothyroidism in type 2 diabetic patients.<sup>16,17</sup>

Whereas the mean serum FT<sub>4</sub> level was significantly lower in uncontrolled diabetic patients than that of controlled diabetic patients. These findings were consistent with that of some other researchers of different countries.<sup>17</sup> Again, the mean serum FT<sub>3</sub> level was non-significantly lower in uncontrolled diabetic patients than that of controlled diabetic patients. Similar finding was observed by Gursoy et al.<sup>17</sup> On the other hand, some researchers found significantly lower serum FT<sub>3</sub> level in uncontrolled diabetic patients than that of controlled diabetic patients.<sup>15</sup> T<sub>4</sub>-5'-deiodinase enzyme is responsible for deiodination of T<sub>4</sub> to T<sub>3</sub>.<sup>26</sup> This enzyme activity was decreased in streptozotocin induced diabetic rats that catalyzes peripheral deiodination of T<sub>4</sub> to T<sub>3</sub> and produces low T<sub>3</sub> state.<sup>20</sup> Pittman et al reported that, reduced level of tissue glutathione is responsible for lowering deiodination in streptozotocin induced diabetic rats.<sup>27</sup> Moreover, thyroid hormone binding inhibitor (THBI), inhibitor of extrathyroidal conversion (IEC) of thyroxine to triiodothyronine and free fatty acid (FFA) are responsible for abnormal thyroid hormone level in uncontrolled diabetic patients.<sup>28</sup>

In the present study, lower levels of thyroid hormones may be due to poor glycemic control. The significant negative correlation of HbA<sub>1c</sub> level with FT<sub>3</sub> and FT<sub>4</sub> levels in uncontrolled diabetic patients are in favor of this statement. Again, serum thyroid stimulating hormone level was found significantly higher in uncontrolled

diabetic patients than controlled diabetic patients. This may be due to negative feedback regulation resulting in increased TSH secretion from the anterior pituitary gland. The positive correlation of serum TSH level with HbA<sub>1c</sub> of the subjects further supports these findings.

### Conclusion

Based on the results of this study, it can be concluded that, hypothyroidism occurs in type 2 diabetic patients which was found only in uncontrolled diabetic patients and this may be due to their poor glycaemic control.

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