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Association Of Thyroid Stimulating Hormone With Glycemic Status In Newly Diagnosed Type 2 Diabetic Patients

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Abstract:
Background: *Prevalence of type 2 diabetes mellitus (T2DM) has increased worldwide to a frightening level in both developed and developing countries over the last decades. Higher prevalence of thyroid dysfunction among diabetic patients has been recognized than that in general population. There is a complex inter-relation between diabetes and thyroid dysfunction which involves biochemical, genetic, hormonal and pathophysiological mechanisms.*
Objective: *Aim of the study was to determine the type of association of thyroid stimulating hormone (TSH) with glycemic status in newly diagnosed T2DM patients.*
Method: *For this cross-sectional study, 100 participants, aged 30 years and above, were enrolled. They were categorized as newly diagnosed T2DM patients and healthy participants according to the diagnostic criteria for DM given by American Diabetic Association, 2019. Blood sample from all the study participants was collected and biochemical tests were performed in the department of Biochemistry and Molecular Biology, Bangabandhu Sheikh Mujib Medical University (BSMMU). After that, collected data was cleaned, entered and analyzed by SPSS software version 20.0.*
Result: *Among the study subjects, serum TSH was found higher, in the newly diagnosed T2DM patients than in the healthy participants. There was significant positive correlation between serum TSH and fasting plasma glucose (FPG), and also between serum TSH and plasma glucose at 2hours after breakfast (PG-2H ABF) in newly diagnosed T2DM patients. Significant positive correlation of serum TSH with FPG (≥8 mmol/L) and PG-2H ABF (≥16 mmol/L) was observed in newly diagnosed T2DM group. This study also revealed that serum TSH was highly influenced by PG-2H ABF in newly diagnosed T2DM patients.*
Conclusion: *Serum TSH had significant positive correlation with FPG and PG-2H ABF in newly diagnosed T2DM patients.*

Keywords*: Type 2 diabetes mellitus, Thyroid dysfunction, Thyroid stimulating hormone, plasma glucose*

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I. Introduction

T2DM has now become the most rapidly developing non-communicable metabolic syndrome. Because it is a significant concern for public health, global leaders have given it the highest priority as one of the most critical non-communicable diseases[1]. The enormous increase in T2DM across all continents may be the result of increasing urbanization, economic growth, and population aging, which causes a greater consumption of unhealthy foods and a more sedentary lifestyle. As well as ethnicity and family history, T2DM has a strong connection with obesity and overweight. This may also be caused by a combination of environmental triggers and multigene predisposition[1]. Thyroid problems are second only to diabetes mellitus in terms of their prevalence[2].

The anterior pituitary gland produces and releases TSH into the bloodstream. By binding to receptors on the cells of the thyroid gland, it regulates the production of the thyroid hormones T_3 and T_4. T_3, the active thyroid

hormone, has negative feedback on hypothalamic tanycytes and thyrotrophs in the pituitary gland. Consequently, in response to sufficient thyroid hormone (TH) levels in tissues, both TRH and TSH secretion decrease. Defective production and secretion of thyroid hormones causes thyroid dysfunction. Symptoms include thyroid gland enlargement (diffuse or nodular), symptoms of thyroid hormone excess (hyperthyroidism), and thyroid gland enlargement with hypothyroidism. This is demonstrated by the circulating levels of TSH[2].

The first report showing the link between DM and thyroid dysfunction was published in 1979[3]. The prevalence of thyroid dysfunction is significantly higher in people with diabetes than in people who are healthy and don't have diabetes[4,5]. 48% of T2DM patients had thyroid dysfunction, whereas it was 6.6% to 9.5% in nondiabetic individuals[6].

The function of thyroid hormones can be affected by DM at two sites: firstly, at the level of hypothalamic control on TSH release from the anterior pituitary, which ultimately causes impairment of TSH response to TRH in case of poorly controlled or uncontrolled diabetes[7]. Secondly, DM affects thyroid function at the time of T_3 conversion from T_4 which takes place in the peripheral tissues. There is a reversible decrease in the hepatic concentration and activity of the T_4 5-monodeiodinase enzyme which occurs due to hyperglycemia in diabetes. This contributes to low serum concentration of T_3, elevated level of reverse T_3 and normal, low or high level of T_4[8]. In addition, hyperinsulinemia associated with insulin resistance (IR) may result in the formation of thyroid nodules by thyroid tissue proliferation. Moreover, some drugs used in the treatment of diabetes have suppressive effect on TSH. Conversely, thyroid disorders also cause alteration in glycemic control and have adverse effect on diabetes[7]. In hypothyroidism, there is reduced synthesis and secretion of insulin. While in hyperthyroidism, insulin excretion would be increased to compensate the increased degradation[9]. Later, excess thyroid hormones reduce the insulin content of the pancreas which may happen due to a reduced level of proinsulin at the mRNA stage[10]. Patients with low level of thyroid hormones are more susceptible to hypoglycemia which causes complications in the management of diabetes[11]. On the other hand, in hyperthyroidism, hyperglycemia develops due to promotion of the gastrointestinal assimilation of glucose, increased insulin resistance, more insulin degradation and stimulation of glycogenolysis[12]. This results in worsening of glycemic control in diabetic patients[13].

It is therefore very common for a person to experience both DM and altered thyroid function at the same time. In most cases, the diagnosis of thyroid abnormality in diabetic patients may be challenging for proper evaluation if it is based solely on clinical manifestations. For instance, if severe diabetic complications or hypothyroidism develop, there may be a problem because patients with these conditions may present similar symptoms and signs, including pallor, weight gain, edema, and fatigue[14]. It is therefore critical to assess the diabetic population with regard to thyroid diseases because one condition can aggravate the other, and if untreated can lead to deterioration of diabetes mellitus, resulting in a variety of complications.

As diabetes mellitus is a major health problem, any disorders that may even be weakly associated with it, needs special attention.

II. Material And Methods

Study design: Cross sectional analytical study.

Place of study: Department of Biochemistry & Molecular Biology, BSMMU.

Study duration: From March, 2021 to January, 2022.

Study population: Study subjects were enrolled from the individual with T2DM (newly diagnosed) and healthy persons accompanying them in Endocrine and Metabolism OPD of BSMMU. Age of the subjects of both groups, were 30 years and above.

Sample size: 100

Sample size calculation: Sample size was calculated by using the following formula:

$$\boldsymbol{n = \frac{(z_\alpha + z_\beta)^2 + ({\sigma_1}^2 + {\sigma_2}^2)}{(\mu_1 - \mu_2)^2}}$$

Putting the values in the above equation, the sample size 'n' was estimated as:

n = 68

So, 68 study subjects were needed to be taken in each group. Though statistically acceptable sample size was 136, due to Covid-19 pandemic and time constraint, sample size was limited to 100 (Group 1= 50 & Group 2= 50) participants in total.

Group 1 (newly diagnosed T2D patients) = 50

Group 2 (healthy subjects) = 50

Subject selection:
Sampling method: Purposive sampling.
Inclusion criteria:
1. For newly diagnosed T2D patients' group: T2D patients aged ≥30 years, who did not take any anti-diabetic therapy.
2. For comparison group: Non-diabetic adults aged ≥30 years

Exclusion criteria:
1. Patients < 30 years,
2. Patients with known thyroid disorders or those with history of neck trauma or surgery or previous exposure of radiation in the neck,
3. Patients on drugs like amiodarone, lithium, interferon alpha, iodides, beta-blockers, carbimazole, propylthiouracil, potassium iodide, Lugol's iodine,
4. Patients who were taking any drugs that may alter glycemic status,
5. Pregnant women,
6. Patients previously diagnosed to have T1DM.

Procedure methodology

Detailed history with other respective information were recorded in the appropriate data sheet. With all aseptic precaution, 6ml venous blood was drawn from ante-cubital vein of the study participants after overnight (10 hours) fasting with the help of a sterile disposable syringe. Then the blood was immediately transferred to an EDTA tube (2ml), a plain tube without anti-coagulant (2ml) and a glucose tube (2ml). Another glucose tube was used to collect blood sample from the participants after 2 hours of taking breakfast. Plasma was collected from blood sample of glucose tube, and serum was collected from the blood in the plain tube after clot formation by centrifuging at 3000 rpm for 10 minutes. Plasma was used for estimation of fasting glucose and glucose at 2 hours after breakfast, whereas HbA1c was estimated in whole blood and TSH in serum. Within 5 hours of collection of blood, laboratory tests for FPG, PG-2H ABF, HbA1c, TSH were done. The entire biochemical tests were performed at the Department of Biochemistry & Molecular Biology, BSMMU.

Laboratory method

1. Estimation of fasting plasma glucose: was done by Glucose Oxidase (GOD-PAP) method (Keston, 1956) using Atellica CH (clinical chemistry) analyzer (Siemens Healthcare Diagnostics Inc., NY, USA).
2. Estimation of plasma glucose-2H ABF: was done by Glucose Oxidase (GOD-PAP) method (Keston, 1956) using Atellica CH (clinical chemistry) analyzer (Siemens Healthcare Diagnostics Inc., NY, USA).
3. Estimation of HbA1c was done by capillary electrophoresis (Klingenberg et al., 2017) using Sebia Capillary analyzer (Capillary 2 flex-piercing system).
4. Estimation of serum TSH: was done by Microparticle Enzyme Immunoassay (MEIA) method using Atellica IM analyzer (Siemens Healthcare Diagnostics Inc., NY, USA).

Statistical analysis

All the collected data was cleaned, entered and analyzed by SPSS software version 20.0. Continuous variables were expressed as either mean ± SD or median with IQR and categorical variables were presented as percentage and frequency. Comparison of various parameters was done by unpaired t-test for normal distribution and Mann-Whitney U test for skewed distribution – as required. Chi-square test was used for the comparison of qualitative data. Spearman rho rank test was done to find out the correlation of FPG, PG level at 2 hours after breakfast & HbA1c with serum TSH level. Multiple linear regression analysis was also performed to assess the influence of glycemic status over serum TSH.

III. Result

Total 100 participants (both T2DM patients and healthy participants) were selected for this study. Patients who were first diagnosed as T2DM (according to American Diabetes Association, 2019 criteria) and who had not yet consumed any anti-diabetic therapy, were taken as newly diagnosed T2DM patients. Age range for newly diagnosed T2DM patients was 30-67 years and for healthy participants was 30-65 years. In newly diagnosed T2DM patients group, 52% were female and 48% were male. On the other hand, 54% were female and 46% were male in healthy participants.

Table no 1: Comparison of serum TSH between two groups (N=100).

Hormone profile	Newly diagnosed T2DM patients (n=50)	Healthy participants (n=50)	p-value
Serum TSH in mIU/L (median with IQR)	2.79 (1.40 - 4.53)	2.24 (1.65 - 3.01)	0.089

p value ≤ 0.05 was considered as significant.

Table no 1 shows newly diagnosed T2DM patients have a raised level of serum TSH in comparison to healthy group, though it was not statistically significant.

Table no 2: Correlation of serum TSH with FPG, PG-2H ABF and HbA1c in newly diagnosed T2DM patients (n=50).

	Parameters	Newly diagnosed T2DM patients (n=50)	
		r value	p value
Serum TSH in mIU/L	FPG (mmol/L)	+0.285	**0.045**
	PG 2H ABF (mmol/L)	+0.341	**0.016**
	HbA1c (%)	+0.140	0.332

p value ≤ 0.05 was considered as significant.

Table no 2 significant positive correlation was observed between serum TSH and FPG (r = +0.285, p = 0.045) and also between serum TSH with PG-2H ABF (r = +0.341, p = 0.016) in newly diagnosed T2DM group, which indicates that serum TSH level was raised with the rise of FPG and PG-2H ABF.

Figure no 1: Correlation of FPG with serum TSH in newly diagnosed T2DM patients (n=50).

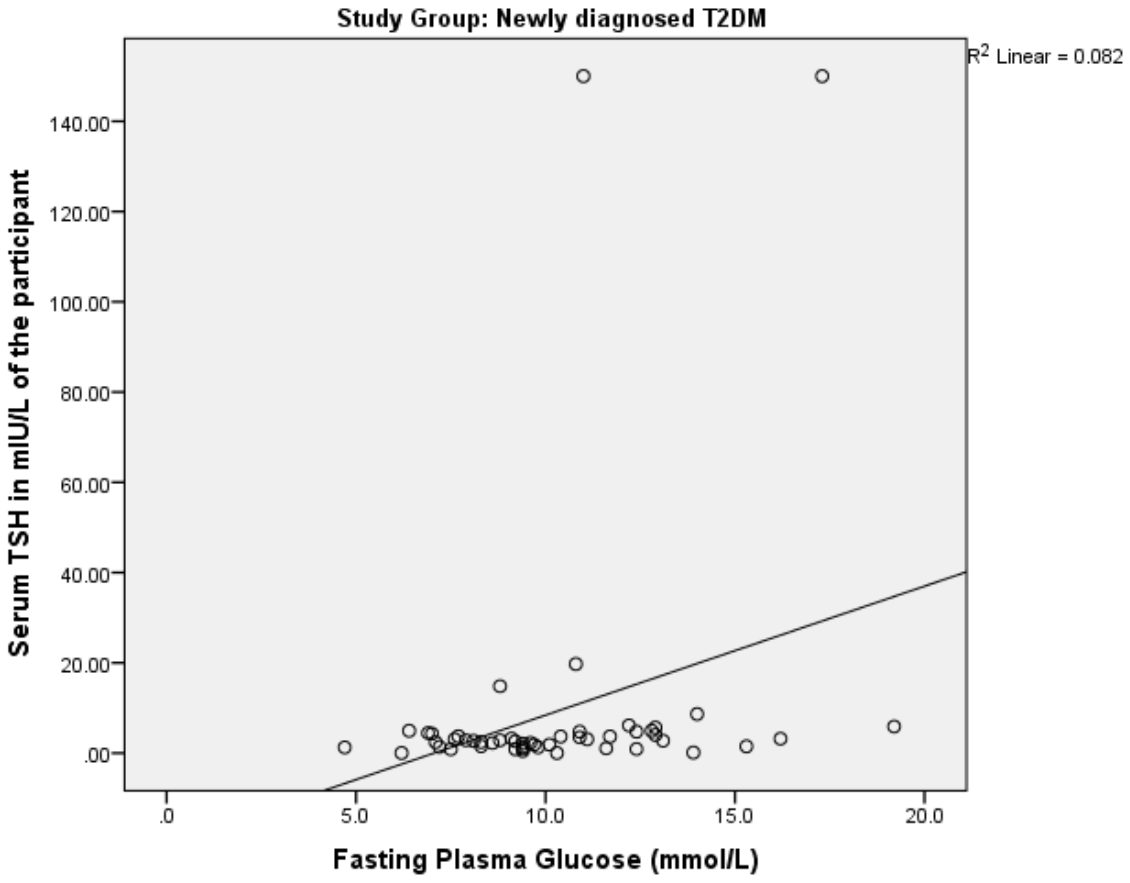

Figure no 1 shows scatter diagram where serum TSH is positively correlated with FPG in newly diagnosed T2DM group (r =+0.285, p = 0.045).

Figure no 2: Correlation of PG-2H ABF with serum TSH in newly diagnosed T2DM patients (n=50).

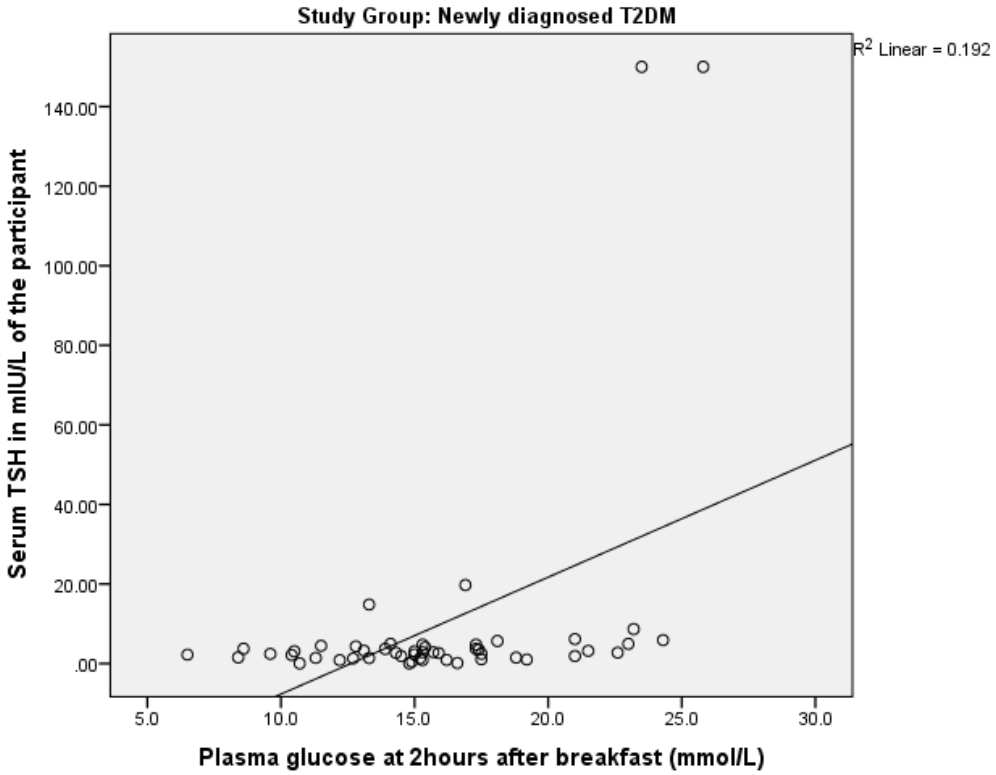

Figure no 2 shows, serum TSH was positively correlated with PG-2H ABF in newly diagnosed T2DM group (r = +0.341, p = 0.016).

Table no 3: Correlation of FPG (<8 & ≥8 mmol/L) with serum TSH in newly diagnosed T2DM patients (n=50).

Parameters	TSH	
	r value	p value
FPG (<8 mmol/L)	+0.091	0.790
FPG (≥8 mmol/L)	**+0.341**	**0.033**

p value ≤ 0.05 was considered as significant.

Table no 3 shows significant positive correlation between FPG (≥8 mmol/L) with serum TSH (r =+0.341, p = 0.033) in newly diagnosed T2DM group. It revealed that if the FPG level was increased ≥8 mmol/L, serum TSH level also increased in T2DM patients.

Table no 4: Correlation of PG-2H ABF (<16 mmol & ≥16 mmol/L) with serum TSH in newly diagnosed T2DM patients (n=50).

Parameters	Serum TSH	
	r value	p value
PG-2H ABF (<16 mmol/L)	+0.085	0.655
PG-2H ABF (≥16 mmol/L)	**+0.530**	**0.016**

p value ≤ 0.05 was considered as significant.

Table no 4 shows significant positive correlation between PG-2H ABF (≥16 mmol/L) with serum TSH (r = +0.530, p = 0.016). It revealed that if the PG-2H ABF level was increased ≥16 mmol/L, serum TSH level also increased.

Table no 5: Correlation of HbA1c (< 9% & ≥ 9%) with serum TSH in newly diagnosed T2DM patients (n=50).

Parameters	Serum TSH	
	r value	p value

HbA1c (< 9%)	+0.070	0.709
HbA1c (≥ 9%)	+0.250	0.312

p value ≤ 0.05 was considered as significant.

Table no 5 shows the correlation of HbA1c (< 9% & ≥ 9%) with serum TSH in newly diagnosed T2DM group. There was no significant correlation among them.

Table no 6: Regression analysis of FPG and PG-2H ABF with serum TSH newly diagnosed T2DM patients (n=50).

Variables	**TSH**	
	β	**p-value**
FPG (mmol/L)	-0.061	0.763
PG-2H ABF (mmol/L)	0.570	**0.008**
HbA1c	-0.155	0.337

p value ≤ 0.05 was considered as significant.

Table no 6 shows, one of the dependent variables, serum TSH was highly influenced by PG-2H ABF (β= +0.570, p = 0.008) in newly diagnosed T2DM patients.

IV. Discussion

Worldwide prevalence of DM is increasing day by day which is frequently associated with morbidity and mortality. Currently 9.3% of the world's population aged 20-79 years are living with diabetes. T2D accounts for around 90% of DM globally[1].

The present study was designed to evaluate the type of association of thyroid function with glycemic status in newly diagnosed T2DM patients. With this aim, 100 participants were enrolled from the outpatient department of Endocrinology and Metabolism, BSMMU. Fifty newly diagnosed T2DM patients (diagnosed according to the criteria of American Diabetic Association, 2019) were categorized as 'Newly diagnosed T2DM patients group'[15]. They were recruited before starting any type of anti-diabetic therapy and having no history of known thyroid abnormality. Another fifty healthy subjects, accompanying the diabetic patients, were taken as 'Healthy group'. In all study subject, the following parameters were done: FPG, PG-2H ABF, HbA1c, serum TSH.

In this study, mean±SD age of the participants were 45.04±10.15 years in newly diagnosed T2DM group and 41.42±10.69 years in healthy participants' group. Females were predominant in both groups (52% in newly diagnosed T2DM patients and 54% in healthy group.). In an Indian study, Vinu et al. (2012) took 80 participants in each group of diabetic and non-diabetic participants, where the mean±SD age was almost similar (43.45±3.18 years and 41.77±2.53 years respectively)[2]. In another study, mean±SD age of diabetic participants was 46.0±9.7 years and that of non-diabetic healthy group was 45.5±7.7 years, which were a little bit higher than this study[16].

In this study, median with IQR of TSH was slightly higher in diabetic group in comparison to that of healthy group. Raghuwanshi et al. (2014) reported significant higher TSH in T2DM patients comparing healthy individuals and agreed with the report of Alam et al. (2013) and Rai et al. (2013)[17,18,19].

Three parameters of glycemic status, namely FPG, PG at 2 hours after breakfast and HbA1c were analyzed to explore the correlation with serum TSH. Among them, Spearman's rho correlation test showed a positive correlation of serum TSH with FPG (r =+0.285, p = 0.045), and also with PG-2H AFB (r =+0.341, p = 0.016) in newly diagnosed T2DM patients. This finding was almost in agreement with the study of Alam et al. (2013) and Raghuwanshi et al. (2014)[17,18]. This study also observed that there was no significant correlation among HbA1c and serum TSH which agreed the study conducted by Abidi et al. (2020)[20]. As HbA1c determines the glycemic control of previous three months, so it might happen to newly diagnosed T2D patients.

This study exposed that serum TSH had significant positive correlation with FPG (≥8 mmol/L) (r =+0.341, p = 0.033) and PG at 2hours after breakfast (≥16 mmol/L) (r = +0.530, p = 0.016) in newly diagnosed T2DM group. So, in case of uncontrolled or poorly controlled DM (when FPG ≥8 mmol/L and PG at 2hours after breakfast ≥16 mmol/L), there may be rise of serum TSH in newly diagnosed T2DM patients.

Finally, multiple regression analysis (among the dependent and independent variables) revealed that serum TSH was highly influenced by PG at 2H ABF (β = +0.570, p = 0.008) in newly diagnosed T2DM patients and it indicates that, serum TSH would be raised by 0.570 units, if PG level at 2H ABF was raised by 1 unit, in case of newly diagnosed T2DM patients.

The above findings may be helpful for the endocrinologists for the early diagnosis of thyroid abnormalities in newly diagnosed T2D patients and thereby will help to achieve adequate glycemic control and delay in the development of complications.

V. Conclusion

It was observed from the study that newly diagnosed T2DM patients are more susceptible to develop altered serum TSH level in comparison to healthy individual. In depth, it was also found that serum TSH had significant positive correlation with FPG and PG-2H AFB in newly diagnosed T2DM patients. Future studies with a larger sample size from different centers with more lab parameters are needed to confirm these findings, and more studies are required to understand the key mechanism.

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