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Original Research Article

Evaluation of Thyroid Hormones Level in Patients with Type 2 Diabetes Mellitus as Compared to Normal Individuals in Nepal

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ABSTRACT

Objective: Diabetes mellitus and thyroid disorders are two of the most common endocrine disorders. Studying the levels of thyroid hormones in patients with type 2 diabetes mellitus can aid in the diagnosis of various thyroid related disorders. The aim of this study was to evaluate thyroid hormones (free tri-iodothyronine [FT3] and, free thyroxine [FT4]) and thyroid stimulating hormone (TSH) in patients with type 2 diabetes mellitus as compared to normal individuals.
Methods: The study was conducted at Norvic International Hospital, Kathmandu, Nepal. The study included thirty patients with type 2 diabetes mellitus attending the Inpatient and Outpatient departments. Serum levels of FT4, FT3 and TSH were estimated as part of a thyroid hormone assay. Glycosylated hemoglobin (HbA1c) and random plasma glucose were estimated to test diabetes.
Results: Statistically significant differences were observed in the mean FT3 activity of normal individuals (4.44 ± 0.82) and patients with type 2 diabetes mellitus (3.37 ± 1.14; P =0.000). Statistically significant differences were also observed in the mean FT4 activity of normal individuals (1.45 ± 0.39) and patients with type 2 diabetes mellitus (1.1± 0.335; P=0.002). Statistical differences in the mean TSH activity were also observed between normal individuals (3.56 ± 2.50) and patients with type 2 diabetes mellitus (5.52 ± 2.41; P=0.003). A positive correlation between TSH and HBA1c (0.397) and a negative correlation between FT3 and HbA1c (-0.508) was found.
Conclusions: Thyroid hormone levels in patients with type 2 diabetes mellitus are perturbed with an increase in TSH and decrease in FT3 and FT4. Therefore this study suggests hypothyroidism in patients with type 2 diabetes mellitus.

Keywords: Type 2 Diabetes Mellitus, Free Tri-iodothyronine, Free Tetra-iodothyronine, Thyroid Stimulating Hormone, and Glycosylated Hemoglobin.

INTRODUCTION

The term diabetes is derived from the Greek word [*Dia*; pass through and *bainein*; to go]. Hence, diabetes literally means to pass through. In this condition, the body is unable to utilize carbohydrate, mostly glucose as an energy source leading to increased glucose level in the blood and is characterized by chronic hyperglycemia associated with disturbances in protein and lipid metabolism on account of absolute or relative deficiency or inefficiency of insulin. [1] The rate of diabetes among the general population is constantly increasing and has reached an alarming state of concern.

Diabetes mellitus is broadly classified into two main types;

- Type I diabetes mellitus: It is also known as immune mediated diabetes, insulin-dependent diabetes or juvenile mediated diabetes. It accounts for 5-10% of diabetes mellitus and results due to

autoimmune destruction of pancreatic B-cells.

- Type II diabetes mellitus: It is also known as non-insulin dependent diabetes or adult onset diabetes. It accounts for 90-95% of diabetes mellitus and occurs as a result of insulin resistance and progressive insulin deficiency. [2]

International Diabetes Federation (IDF) had estimated a 72.1 million people in South East Asia had diabetes in 2014 and this number is expected to increase up to 123 million by 2040. Also according to the data compiled in IDF, sixth edition, 2013, Diabetes caused 5.1 million deaths in 2013. This corresponds to the death of a person every six seconds due to diabetes. [3]

Diabetes cases are increasing in the modern world due to an increasing prevalence of obesity and sedentary lifestyle. [4] Type II Diabetes mellitus results as a result of insulin resistance combined with β- cell dysfunction. However, β- cells are initially functional and the level of insulin in the blood may vary from above normal to below normal. [2] Metabolic changes observed in patients with T2DM are mostly due to insulin resistance in liver, muscle and adipose tissue. Hyperglycemia is observed due to an increased glucose production from liver and decreased peripheral use as a result of insulin resistance. [5] Type 2 Diabetes Mellitus develops gradually without any specific symptoms and is characterized late only once the other conditions affecting various organs of an individual. [6] Individuals with diabetes mellitus are presented with classical symptoms of frequent urination, thirst, and hunger. [7]

On the other hand thyroid diseases had also became common among general population affecting 750 million people worldwide according to the data provided by World health organization. [8] Thyroid hormones are produced by a butterfly-shaped thyroid gland located in the lower anterior neck. [9] Thyroxine (T4) is the primary hormone secreted by the thyroid gland which is relatively inactive and is converted to the highly active form triiodothyronine (T3) by the enzyme thyroxine 5- deiodinase. [10]

The thyroid hormones are insulin antagonists and influence the action of insulin indirectly which could be responsible for the occurrences of low thyroid hormone levels in diabetic mellitus patients. [11] Insulin, an anabolic hormone has been found to enhance the levels of FT4 and suppresses the levels of FT3 by inhibiting hepatic conversion of T4 to T3.Therefore; this may be the reason for low FT3 in type 2 diabetes mellitus patients. 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 T4 to T3 in the peripheral tissue. [12]

A study by Panneerselvam et al. showed that serum levels of T3, T4, FT3 and FT4 were significantly lower in diabetic subjects as compared to the non-diabetic subjects while serum level of TSH was found to be significantly higher in type 2 diabetes mellitus patients as compared to normal individuals. [11]

Another study by Islam S et al. showed serum level of FT3 was significantly lower in type 2 diabetic patients as compared to the non-diabetic individuals. While FT4 and TSH level did not show any statistical difference between type 2 diabetic patients as compared to normal individuals. [13]

Therefore, this study is an effort to evaluate thyroid hormones; FT4, FT3, and TSH between type II diabetes mellitus patients and normal individuals.

METHODS AND MATERIALS

Subject Selection

The study was conducted at Norvic International hospital located at Thapathali, Kathmandu, Nepal. Study was conducted among thirty type 2 diabetes mellitus patients and thirty normal individuals attending Inpatient and Outpatient

department. Serum free thyroxine (FT4), free tri-iodothyronine (FT3) and thyroid stimulating hormone (TSH) were estimated by Electrochemiluminescence method as a part of thyroid hormone assay. Glycosylated hemoglobin (HbA1c) was measured using Boronate Affinity method and Random plasma glucose was estimated by using Hexokinase method to test diabetes.

Inclusion Criteria

In the study we have included only those patients who are having random plasma glucose levels > 200 mg/dl and HbA1c level more than 6.5 %.

Exclusion Criteria

Known diabetic patients who were under insulin therapy or those taking oral hypoglycemic drugs.

Sample Collection

Blood samples were collected through antecubital vein from all subjects into following vials for various biochemical tests:

1. Fluoride oxalate vial for random plasma glucose estimation
2. EDTA vial for Glycosylated hemoglobin (Hb_1Ac) estimation.
3. Silica gel vial for TSH, FT3, and FT4 estimation.

Statistical analysis:

Mean ± SD were calculated for all the parameters and were compared by Student's t-test and correlated by calculating Pearson's correlation coefficient using SPSS calculator. P-values considered significant were as follows:

P <0.05 – Significant

P <0.01 – Highly Significant

RESULTS

Table 1: Comparison of serum free tri-iodothyronine (FT3) activity between normal individuals and type 2 diabetes mellitus patients using Student's t-test.

Parameter	Normal Individuals (n=30) Mean ± SD	Diabetic patients (n=30) Mean ± SD	p-value
Serum FT3 activity (pmol/L)	4.44 ± 0.82	3.37 ± 1.14	0.000***

P < 0.001 *** P < 0.01 ** P < 0.05 * NS = Non significant

Statistically significant differences were observed in the mean serum FT3 activity of normal individuals (4.44 ± 0.82) and type 2 diabetic patients (3.37 ± 1.14). (p=0.000) when two tailed test was applied.

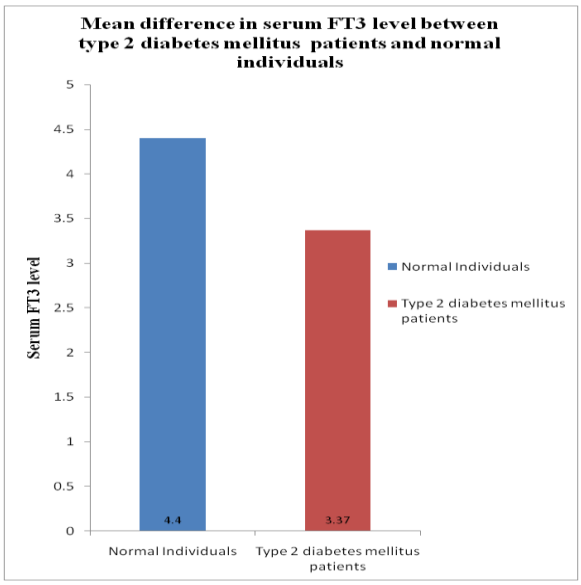

Fig 1: Figure showing mean difference in serum FT3 level between normal individuals and type 2 diabetes mellitus patients.

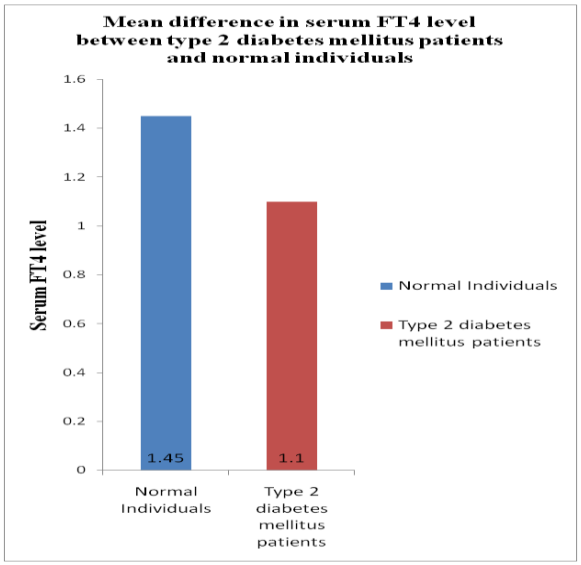

Fig 2: Figure showing mean difference in serum FT4 level between normal individuals and type 2 diabetes mellitus patients.

Table 2: Comparison of serum free tetra-iodothyronine (FT4) activity between normal individuals and type 2 diabetes mellitus patients using Student's t-test

Parameter	Normal Individuals (n=30) Mean ± SD	Diabetic patients (n=30) Mean ± SD	p-value
Serum FT4 activity (ng/dL)	1.45 ± 0.39	1.1± 0.335	0.002**

P < 0.001 *** P < 0.01 ** P < 0.05 * NS = Non significant

Statistically significant differences were observed in the mean serum FT4 activity of normal individuals (1.45 ± 0.39) and type 2 diabetic patients (1.15 ± 0.33). (p=0.002) when two tailed test was applied.

Table 3: Comparison of serum Thyroid Stimulating Hormone (TSH) activity between normal individuals and type 2 diabetes mellitus patients using Student's t-test

Parameter	Normal Individuals (n=30) Mean ± SD	Diabetic patients (n=30) Mean ± SD	p-value
Serum TSH Activity (uIU/L)	3.56 ± 2.50	5.52 ± 2.41	0.003**

P < 0.001 ***P < 0.01 ** P < 0.05 * NS = Non significant

Statistically significant differences were observed in the mean serum TSH activity of normal individuals (3.56 ± 2.50) and type 2 diabetic patients (5.52 ± 2.41). (p=0.003) when two tailed test was applied.

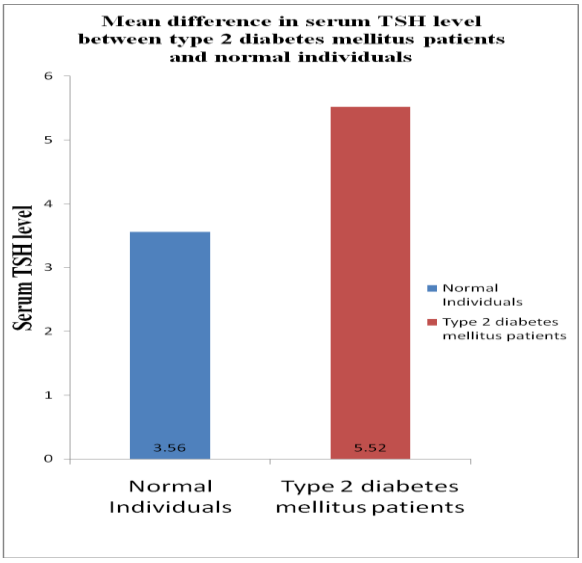

Fig 3: Figure showing mean difference in serum TSH level between type 2 diabetes mellitus patients and normal individuals.

Table 4: Tabular representation of different parameters among type 2 diabetes mellitus patients showing Pearson correlation coefficient (r) and p value

Parameters	r-value	p-value
FT3- HbA1c	-0.508	0.004
TSH- HbA1c	0.397	0.03

After applying Pearson's correlation coefficient it was found that there is a negative correlation between serum FT3 activity and HbA1c (r=-0.508) and positive correlation between serum TSH activity and HbA1c (r =0.397).

DISCUSSION

This study was done with the purpose to evaluate the levels of serum FT3, FT4, and TSH in type 2 diabetes mellitus patients.

Diabetes mellitus is a common health problem affecting millions of population worldwide. The root cause of diabetes mellitus is defective production or ineffective action of insulin that controls glucose, fat and amino acid metabolism. [14] Adoption of a sedentary lifestyle, the consumption of non-traditional foods, and a genetic predisposition to the disease are some other factors contributing to the development of diabetes mellitus. [15]

Glycosylated hemoglobin, also known as hemoglobin A1C, HbA1c, A1C or Hb1c, is a form of hemoglobin used primarily to identify the average plasma glucose concentration over a prolonged period of time. [16] During the normal 120-day life span of the red blood cell (RBC), glucose molecules react with hemoglobin, forming glycated hemoglobin. Once a hemoglobin molecule is glycated, it remains in this form. Red blood cells (RBCs) that contain the hemoglobin circulate in the bloodstream for three to four months before being broken down and replaced. A buildup of glycated hemoglobin within the red blood cell, therefore, reflects the average level of glucose to which the cell has been exposed during its life cycle. Thus, A1C readings higher than about 6% indicate higher than normal amounts of glucose roaming the blood stream in the past 120 days. [17]

Thyroid gland is one of the largest endocrine gland in the body. It is a butterfly shaped organ made up of two lobes connected via the isthmus. It is situated on the anterior side of the neck and around trachea and larynx. [18] Thyroid hormone is produced by the thyroid gland, which consists of follicles in which thyroid hormone is synthesized through iodination of tyrosine residues in the glycoprotein thyroglobulin. [19,20] Thyroid stimulating hormone (TSH), secreted by the anterior pituitary in response to feedback from

circulating thyroid hormone, acts directly on the TSH receptor on thyroid gland to produce thyroid hormones (T3 and T4). [21] Thyroid hormone is essential for normal development, growth, neural differentiation, and metabolic regulation in mammals. [22-24]

The association between diabetes and thyroid dysfunction had been recognized since late 90's and this has emphasized the importance of screening of diabetic patients to identify thyroid diseases. [25,26] A number of the studies have reported the prevalence of thyroid dysfunction among diabetes patients to be between 2.2 to 17%. [27] However, few studies have observed the very high prevalence of thyroid dysfunction in diabetes i.e. 31 % and 46.5% respectively. [28] Diabetes patients have a higher prevalence of thyroid disorders than the normal population. [29] Varieties of thyroid abnormalities are known to co-exist and interact with diabetes mellitus. The frequency of hyperthyroidism and hypothyroidism in patients with diabetes has varied from 3.2 % to 4.6 % and 0.7 % to 4.0 % respectively. [30] In hyperthyroidism, increased levels of serum FT3 and FT4 is observed while serum TSH is significantly low. Similarly hypothyroidism is characterized by decreased level of serum FT3 and FT4 with an increase in the level of serum TSH.

This study was conducted among 30 known type 2 diabetes mellitus patients who were not under any oral hypoglycemic drugs or insulin therapy and 30 normal individuals taken as controls. The mean values of serum FT3 in our present study was found to be (3.37 ± 1.14) in type 2 diabetes mellitus patients. Similarly the mean value of serum FT3 in normal individuals was found to be (4.44 ± 0.82). Therefore, our present study suggests significantly low level of serum FT3 activity in type 2 diabetes mellitus patients as compared to normal individuals (p=0.0000). A study by Islam S et al, [13] Singh G et al. [31] also shows level of FT3 to be significantly lower in type 2 diabetic mellitus patients when compared to normal individuals.

Mean values of serum FT4 in our present study was found to be (1.1± 0.335) in type 2 diabetes mellitus patients and (1.45±0.39) in normal individuals (p=0.002).Our result suggests significantly lower level of serum FT4 activity in type 2 diabetes mellitus patients as compared to normal individuals. This is comparable to the previous study by Singh G et al. (31) where serum FT4 level was significantly lower in type 2 diabetes mellitus patients as compared to normal individuals. However, a study by Islam S et al. [13] shows no statistically significant difference in serum FT4 level between type 2 diabetic individuals and normal individuals.

Similarly, mean values of serum TSH in our study was found to be (5.52 ± 2.41) in type 2 diabetic patients and (3.56 ± 2.50) in normal individuals (p=0.003). This statistical value suggests significantly higher level of serum TSH activity in type 2 diabetes mellitus patients as compared to normal individuals. A study by M Anita Devi et al. [32] also showed the level of TSH to be significantly higher in diabetes mellitus patients indicating hypothyroidism in the diabetic patients which agrees to our findings. A study by Panneerselvam et al. [11] showed significantly higher level of TSH in type 2 diabetes mellitus patients than in normal individuals. In contrast to our finding, a study by Islam S et al. [13] and Udiong CEJ et al. [33] showed no statistically significant difference between type 2 diabetics and normal individuals.

On the other hand, Pearson's correlation coefficient of free triiodothyronine (FT3) with HbA1c showed inverse correlation (-0.508). A study by Panneerselvam et al. [11] also showed a negative correlation between FT3 and HbA1c level which indicates significantly lower level of serum FT3 in type 2 diabetes mellitus patients as compared to normal individuals. Another study by Islam S et al. [13] also showed significant inverse correlation between serum FT3 levels and HbA1c levels.

Similarly, in this study Thyroid stimulating hormone (TSH) showed positive correlation with HbA1c (0.397). A study by Velija-Asimi et al. [34] and Billic-Komarica et al. [35] also shows positive correlation between serum level of TSH and the level of HbA1c, which agrees to our findings.

CONCLUSION

This study suggests high prevalence of hypothyroidism in type 2 diabetes mellitus patients as compared to normal individuals. Finding in our study is limited as thyroid hormones have different normal ranges between males, females, pregnant women, and non-pregnant women. Therefore, further studies needs to be carried out for the interpretation of thyroid hormone in type 2 diabetes mellitus patients.

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