International Journal for Research in Engineering Application & Management (IJREAM)
ISSN : 2454-9150 Vol-05, Issue-02, May 2019

Prevalence of Thyroid Dysfunction in type 1 Diabetic Punjabi population

Vikas Gupta, Assistant Professor, Dept of Biotechnology, DAV College, Amritsar, Punjab, India

Email ID: bio_vic@yahoo.com

Diabetes mellitus (DM) is a common endocrine metabolic disorder, characterized by hyperglycemia resulting from a variable interaction of hereditary and environmental factors. DM is commonly associated with thyroid dysfunction. The aim of the present study was to evaluate the frequency of thyroid dysfunction in subjects with type 1 diabetes. To meet the above objective blood sample was collected from 20 type 1 diabetic subjects and 100 healthy non diabetic subjects and investigated for total triidothyronine (T3), total thyroxine (T4), free triidothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), plasma glucose fasting(FPG) and glycosylated hemoglobin (HbA1c). The level of T3, T4, FT3 and FT4 were significantly lower while the level of TSH was significantly higher in type 1 diabetics as compared to non-diabetics. The prevalence of thyroid dysfunction among type 1 diabetic Punjabi population is very high (25%) with primary hypothyroidism being more common. Failure to recognize the presence of abnormal thyroid hormone level in type 1 diabetes may be a primary cause of poor management often encountered in some treated type 1 diabetics. There is therefore need for the routine assay of thyroid hormones in type 1 diabetic, particularly in those patients whose conditions are difficult to manage.

Keywords — Diabetes , Hypothyroidism , FT3, FT4, T3,T4,TSH

I. INTRODUCTION

Type 1 diabetes is an autoimmune disease where the host immune system destroys the insulin producing β-cells in the pancreas. This type of diabetes accounts for 10-15% of all people with the disease. It can appear at any age, although commonly under 40 and is triggered by environmental factors such as viruses, diet or chemicals in people genetically predisposed. People with type 1 diabetes must be injected with insulin several times a day and follow careful diet and exercise plan [1].

Next to diabetes, thyroid disease is other common endocrine problem present in India. It is second only to diabetes as the most common condition to affect the endocrine system. Thyroid is a butterfly-shaped gland located in the neck just below the Adam's Apple and above the collar-bone. It produces two hormones, thyroxin (T_4) and triiodothyronine (T_3) which enters the blood stream and affect the metabolism of the heart, liver, muscles and other organs. Thyroid gland operates as a part of feed back mechanism involving the hypothalamus and the pituitary gland which are located in the brain. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary gland to secrete thyrotropin or thyroid stimulating hormone (TSH). TSH increases iodide uptake and oxidation that leads to organification and coupling in thyroid gland. These are necessary steps to produce the thyroid hormones T_4 and T_3. Of thyroid hormones secreted 90% is T_4 and 9% is T_3. T_3 is derived from deiodination of T_4; therefore 80% of circulating T_3 is obtained from T_4. Excessive T_4 and to a small degree T_3 circulating in the serum inhibits secretion of TSH and TRH, thereby completing the feedback cycle [2].

Thyroid hormones exert profound effect in the regulation of glucose homeostasis. These effects include modifications of circulating insulin levels and counter regulatory hormones, intestinal absorption, hepatic production and peripheral tissues (fat and muscle) uptake of glucose. It has long been known that thyroid hormones act differentially in liver, skeletal muscle and adipose tissue, the main targets of insulin action. While thyroid hormones oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis [3] they up regulate the expression of genes such as GLUT-4 and phosphoglycerate kinase, involved in glucose transport and glycolysis respectively, thus acting synergistically with insulin [4] in facilitating glucose disposal and utilization in peripheral tissues.

There are two main disorders of thyroid gland, hypothyroidism or an under active thyroid gland and hyperthyroidism or an overactive thyroid gland. It adversely affects diabetic control and is commonly found in most forms of Diabetes Mellitus (DM) which

 DOI : 10.35291/2454-9150.2019.0022

is associated with advanced age in type 2 diabetes and autoimmune disease in type 1 diabetes. DM appears to influence thyroid functions at two sites; firstly at the level of hypothalamic control of TSH release and secondly at the conversion of T_4 toT_3 in the peripheral tissue. Marked hyperglycemia causes reversible reduction of the activity and hepatic concentration of T_4 -5 deiodinase, low serum concentration of T_3, elevated levels of reverse T_3 and low, normal or high levels of T_4 [5]. T_4 (total and free) and T_3 concentration may be inappropriately normal when hyperthyroidism is present in patient with poorly diabetic control making some diagnostic difficulties which is supported by suppressed serum basal TSH or an absolutely flat response to TRH [6]. In euthyroid diabetic patient serum T_3 levels and basal TSH levels with its response to TRH is influenced by glycemic status and poorly controlled diabetes may induce reversible 'low T_3 state' [7].

Hyperthyroidism may be present in diabetic patients with or without thyroid enlargement in the presence of unexplained weight loss, supraventriculars tachycardia, increased body temperature, heat intolerance, tremor, unexplained increase in insulin requirement, ketoacidosis and uncontrolled diabetic state despite strict antidiabetic treatment. Sulfonylurea commonly prescribed for control of diabetes, has an important goiterogenic affect on thyroid gland and may affect the prevalence of goiter in diabetic patients.

Thyrotoxicosis is diabeticogenic factor and long term thyrotoxicosis has been shown to cause β-cell dysfunction. In hypothyroidism there is reduction in the rate of glucose absorption, gluconeogenesis and glucose production (and utilization) and glycogen synthesis (and degradation) leading to increased glycogen level. Additionally, insulin half-life will be prolonged with increase in its level and reduction in insulin requirement. Glucose level will be stabilized during treatment of hypothyroidism but the risk of recurrent hypoglycemia will increase if insulin dose is not decreased. In hyperthyroidism there is elevation in the rate of glucose absorption, production (and utilization) and glycogen synthesis (and degradation) leading to decreased glycogen level [7] but insulin resistance, degradation and requirements are increased and there is increased secretion with exaggerated effects of glycogen and adrenaline on the liver. All these changes may lead to diabetic ketoacidosis in state of insufficient insulin supply. In patients with undetected DM, hyperthyroidism can unmask diabetes because glucose levels may be elevated. For these reasons the dosage of oral antidiabetic drugs (OAD) and insulin should be increased in diabetic patients with thyroid disease.

Thyroid disorders are widely common amongst diabetic patients with variable prevalence among the different populations. The NHANES III observed an increased frequency of thyroid dysfunction with advancing age and prevalence of thyroid disease was higher in women as compared to men and was more frequent in diabetic subjects as compared to non diabetic [8]. Another study demonstrated prevalence of 13.4% of thyroid diseases in diabetics with highest prevalence in type 1 female diabetics (31.4%) and lowest prevalence in type 2 male diabetic (6.9%)[9]. A prevalence of 12.3% was reported among Greek diabetic patients [10]. In another study a prevalence of 16% was reported in Saudi patients with type 2 diabetic [11]. In Jordan, a study reported that thyroid dysfunction was present in 12.5% of type 2 patients [12]. However, thyroid disorders were found to be more common in subjects with type 1 diabetes compared to those with type 2 diabetes.

The relationship between type 1 diabetes and thyroid dysfunction has not been extensively studied in Punjab although the prevalence of diabetes mellitus is very high and increasing. It is possible that there are diabetic patients who might have thyroid dysfunction which may greatly affect their glycemic control. Due to the lack of adequate information about the two conditions, preventive management is difficult to plan.

Keeping the above in view the objectives of the present study are to estimate & compare the levels of thyroid hormones (T_3, T_4, FT_3, FT_4 and TSH) in type 1diabetics and non diabetics subjects and to evaluate the prevalence of thyroid dysfunctions in diabetic and non diabetic control subjects not previously diagnosed having thyroid dysfunction.

II. Materials and Methods

The subjects were selected from the cases presenting with type 1 diabetes in the OPD and ward of department of medicine, in Civil Hospitals of Kapurthala, Jalandhar and Amritsar. An informed verbal consent was taken from each and every patient.

The study population consisted of 20 type 1 diabetic and 100 non diabetic subjects. The criteria for diagnosis of type 1 diabetes were the American Diabetic Association criteria; FPG of 110 mg/dl, random blood sugar of 200 mg/dl or taking hypoglycemic drugs and/or using insulin and did not have any episodes of ketosis in the past. All patients with diseases that may affect thyroid function were excluded.

The non diabetes volunteers without history of DM whose FPG were less than 110 mg /dl on two occasions were taken as the control samples. These volunteers included non-diabetic subjects who came in the hospitals for routine

 DOI : 10.35291/2454-9150.2019.0022

checkups as advised by their attending physicians. The controls were not taking any drugs.

Venous blood sample were withdrawn and assayed for thyroid function such as FT_4, FT_3, T_3, T_4, TSH and other biochemical investigation such as FPG and HbA1c. The serum levels of FT_3 (normal range 1.5-4.2 pg /ml), FT_4 (normal range 0.8-1.68 ng/dl), T_3 (normal range 70-210 ng/dl), T_4 (normal range 5.2-11.8 µg/dl) and TSH (normal range 0.2-5.2 µiu/ml) were determine by electrochemiluminous method on Elecsys 2010. FPG (normal range 70-110mg/dl) and HbA1c (normal range 4.2-6.2%) were determined on semi automated clinical chemistry analyzer. The following guidelines for detection of thyroid dysfunction were considered: 1) Normal – when FT_3, FT_4, T_3, T_4 and TSH were within the normal range. 2) Primary hypothyroidism – when TSH is more than 5.2 mIU/L and FT_3, FT_4, T_3, T_4 is less than the normal value. 3) Primary hyperthyroidism - when TSH is less than 0.2 mIU/L and FT_4, FT_3, T_3, T_4 is more than the normal values. 4) Subclinical hypothyroidism – when TSH is more than 5.2 mIU/L and FT3, FT_4, T_3, T_4 is within the normal range. 5) Subclinical hyperthyroidism – when TSH is less than 0.2 mIU/L and FT_3, FT_4, T_3, T_4 are within the normal range.

Statistical Analysis

The results obtained from the above investigation were analysed and expressed as mean ± SD. The comparison was done by student t test on no. of variable of each parameter using SPSS version 10.

III. RESULTS

Among the 20 type 1 diabetic subjects, 12 were male and 8 were female and among the 100 non-diabetic subjects 48 were male and 52 were females. The levels and comparison of mean of FPG and HbA1c in type1 diabetic and non-diabetic subjects are shown in Table 1. The mean FPG levels (151.4±12.55 mg/dl) in type 1 diabetic subjects was very significantly (p=<.0001) higher than the mean (88.52±6.72 mg/dl) value in non-diabetic subjects. Similarly mean value of HbA1c (7.01±0.46 %) in type 1 diabetic subjects was very significantly (p=<.0001) higher than non-diabetic subjects (5.01±.22 %).

Table 1: Levels of FPG and HbA1c in type 1 diabetic and non-diabetic Subjects

Parameter	Type 1diabetic (N = 20)	Non – diabetic (N = 100)	t value	S E	p value
	Mean ± SD	Mean ± SD			
FPG (mg/dl)	151.4 ± 12.55	88.52 ± 6.72	32.27	1.94	<.0001*
HbA1c (%)	7.01 ± 0.46	5.01 ± 0.22	29.87	0.06	<.0001*

*Highly Significant

Thyroid related Tests

The levels and comparison of mean serum FT_3, FT_4, T_3, T_4 and TSH in type 1 diabetic and non-diabetic groups are shown in Table 2. The mean (2.01±0.45 pg/ml) serum free T_3 levels in type 1 diabetic subjects was significantly (p=<.0001) lower than the mean (2.87±0.32 pg/ml) in non-diabetic subjects. The mean (0.97±0.19 ng/dl) serum free T_4 in type 1 diabetic subjects was lower than mean (1.23±0.10 ng/dl) in non-diabetic subjects and this differences was statistically very significant (p=.0001). The mean serum T_3 in type 1 diabetic and non-diabetic subjects was (108.1±25.28 ng/dl) and (144.68±12.94 ng/dl) respectively. Serum T_3 value was significantly (p=<.0001) different when compared between two groups. The mean (6.37±1.03 µg/dl) serum T_4 levels in type 1 diabetic subjects was significantly (p=<.0001) lower than the mean (8.07±.76 µg/dl) in non-diabetic subjects. There was very high significant (p=<.0001) difference between the mean (6.52±5.32µIU/ml) serum TSH levels in type 1 diabetic subjects compared with mean (2.29±1.60 µIU/ml) in non-diabetic subjects.

Table 2: Levels of serum FT_3, FT_4,T_3,T_4,TSH in type 1 diabetic and non-diabetic groups

Parameters	Type 1diabetic (N = 20)	Non-diabetic (N = 100)	t value	S E	p value
	Mean ± SD	Mean ± SD			
Serum freeT_3(pg/ml)	2.01 ± 0.45	2.87 ± 0.32	10.198	0.084	<0.0001*
Serum free T_4 (ng/dl)	0.97 ± 0.19	1.23 ± 0.10	8.906	0.029	<.0001*
Serum T_3 (ng/dl)	108.1 ± 25.28	144.68 ± 12.94	9.572	3.821	<.0001*
Serum T_4 (µg/dl)	6.37 ± 1.03	8.07 ± 0.76	8.572	0.198	<.0001*
Serum TSH (µIU/ml)	6.52 ± 5.32	2.29 ± 1.60	6.669	0.634	<.0001*

* Highly Significant

Prevalence of thyroid disorders in diabetes mellitus

In our study the frequency of thyroid dysfunction was 5 (25%) in diabetic subjects as compared to 4 (4%) in non-diabetic subjects .

 DOI : 10.35291/2454-9150.2019.0022

Table 3: Distribution of thyroid disorders according to gender in type 1 diabetes and non diabetic subjects		
Group	Number of subjects having thyroid disorders in	
	Type 1 diabetes mellitus(N = 20)	Non Diabetics (N = 100)
Male	2 (10%)	1 (1%)
Female	3 (15%)	3 (3%)
Total	5 (25%)	4 (4%)

When the subjects were sub grouped on the basis of gender it was observed that prevalence of abnormal thyroid function was more in females as compare to males type 1 diabetic subjects (Table 3).

The subjects with thyroid dysfunction were further subgrouped into subclinical and primary thyroid diseases (Table 4). In type 1 diabetic subjects there were two cases of sub clinical hypothyroidism and three cases of primary hypothyroidism. In case of non-diabetic group four subjects were having sub clinical hypothyroidism. There was no case of subclinical and primary hyperthyroidism in both the groups.

Table 4: Type of thyroid disorders according to gender in type 1 diabetic and non diabetic subjects			
Types of diabetes along with the gender		Types of thyroid disorders*	
		Subclinical Hypothyroidism	Primary Hypothyroidism
Type 1diabetic (N=20)	Male	1	1
	Female	1	2
Non-diabetic (N=100)	Male	1	0
	Female	3	0

*No case of Subclinical and Primary Hyperthyroidism

IV. Discussion

The mean serum FT_3, FT_4, T_3, T_4 were significantly lower (P=<.0001) in diabetic compared to non-diabetic control subjects, while the mean TSH level were significantly higher in diabetic compared to non-diabetic subjects (Table 2). These are in agreement with the number of reports on TSH level in type 1 and type 2 diabetes mellitus and many of them have recorded elevated TSH level [9,13,14]. The overall prevalence of thyroid disease in Scotland was found to be 13.4%, with prevalence of 31.4% in type 1 diabetic females, and lowest in type 2 diabetic males (6.9%)[9]. The Explanation for this finding is that the thyroid hormones, triiodothyroine and tetraiodothyroine are insulin antagonists that also potentiate the action of insulin indirectly [15]. In diabetic patients, the nocturnal TSH peak is blunted and TSH response to TRH is impaired [16] which is responsible for the occurrence of low thyroid hormones level in diabetics. The abnormal thyroid hormones levels found in diabetes is attributed to the presence of thyroid hormones binding inhibitor (THBI), an inhibitor of extra thyroidal conversion enzyme (5'-deiodinase) of T_4 to T_3 and dysfunction of the hypothalamus-pituitary-thyroid axis [17]. These situations way prevail in diabetics & would be aggravated in poorly controlled diabetics. Stress, which is associated with diabetes, may also cause changes in the hypothalamus anterior pituitary axis in these diabetics. It appears that the presence of subclinical hypothyroidism and hypothyroidism may results from hypothalamus-hypohyseal- thyroid-axis disorders as suggested by [18].

There are few studies on the prevalence of thyroid dysfunction in diabetes. Some studies have targeted only type 1 diabetes, while other only type 2 diabetes. The prevalence of thyroid dysfunction varies among different population. The present study concluded 25% of diabetic subjects had thyroid dysfunction (Table 3). When we compared our study with different studies from different parts of the world the prevalence of thyroid dysfunction among diabetes mellitus varies. [19] reported prevalence of 10.8% thyroid dysfunction in DM patient while [20]reported that 46.5% of diabetic patient have thyroid disorder but all these studies showed high incidence of thyroid dysfunction among diabetic as compared to control population.

The prevalence of thyroid dysfunction were more in female as compared to male in our study (Table 3). These observations are consistent with the other studies [19,21]. This finding is probably associated with the higher prevalence of obesity recorded in female diabetics. Insulin, which is used in treating diabetes and is produced in normal quantities or in excess, has been associated with increased anabolic activity.

Among 20 diabetic subject studied, 25% had lower thyroid hormone level where as in non-diabetic subjects, only 4% had lower thyroid hormone level (Table 3). Our study is being supported by the other studies by[18,20,21,22]on thyroid disorder in diabetes showing the high prevalence of hypothyroidism. (both clinical and sub clinical hypothyroidism) as compared to hyperthyroidism. The presence of both raised and low levels of thyroid hormones in diabetes in this study may also be due to modified TRH synthesis and release [17] and may depend on the glycemic status of diabetics studied. Glycemic status is influenced by insulin which in known to modulate TRH and TSH.

The abnormal thyroid hormone level may be out came of various medication the diabetes were receiving for example it is known that insulin an anabolic hormone enhances the level of FT_4, while it suppresses the level of T_3 by inhibiting hepatic conversion of T_4 to T_3. On the other hand, some of the oral hypoglycemic agents such as the phenythioureas are known to suppress the level of FT_4 and T_4 while causing

 DOI : 10.35291/2454-9150.2019.0022

raised level of TSH [17]. These situations may explain the finding of low or raised thyroid hormones status in diabetic subjects. Nevertheless the situations in these diabetics does not seen to follow the pattern previously recorded in other non thyroid diseases such as liver diseases and Cushing syndrome where low thyroid hormone level were recorded. The thyroid hormones, triiodothyronine and tetraiodothyronine are insulin antagonists that also potentiate the action of insulin indirectly. These factors could be responsible for the occurrence of low thyroid hormones level in some diabetes.

V. REFERENCES

[1] Nederstigt C, Corssmit EP, de Koning EJ, Dekkers OM. Incidence and prevalence of thyroid dysfunction in type 1 diabetes. J Diabetes Complications. 2016 ;30:420-5.

[2] Johnson JL. Diabetes control in thyroid disease. Diabetes spectrum. 2006;19:148-53.

[3] Biondi B, Kahaly GJ, Robertson RP. Thyroid Dysfunction and Diabetes Mellitus: Two Closely Associated Disorders. Endocr Rev. 2019. doi: 10.1210/er.2018-00163.

[4] Clement K, Viguerie N, Diehn M, Alizadeh A, Barbe P, Thalamas C, *et al*. *In vivo* regulation of human skeletal muscle gene expression by thyroid hormone. Genome Res. 2002;12:281-91.

[5] Shah SN. Thyroid disease in diabetes mellitus. J Assoc Phys India. 2007; 32:1057-59.

[6] Cavaleri RR. The effects of non thyroid disease and drugs on thyroid function tests. Medical clinics of North America. 1996;75:27-39.

[7] Donckier JE. Endocrine diseases and diabetes. In: Textbook of diabetes mellitus . Pickup JC, Williams G (eds), Blackwell Publishing Company, Chichester. 2003.

[8] Hollowell JG. Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, *et al*. Serum TSH, T(4) and thyroid antibodies in the United States population (1988 to 1994); National Health and Nutrition Examination Survey (NHANES III).J Clin Endocrinol Metab. 2002;87:489-99.

[9] Perros P, MC Crimm RJ, Shaw G,Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabet. Med. 1995;12:622-27.

[10] Papazafiropoulou A, Sotiropoulos A, Kokolaki A, Kardara M, Stamataki P, Pappas S. Prevalence of thyroid dysfunction among Greek Type 2 diabetic patients attending an outpatients clinic. J Clin Med Res. 2010;2:75-78.

[11] Akbar DH, Ahmed MM, Al-Mughales J. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetic. Acta Diabetol. 2006;43:14-8.

[12] Radaideh AR, Nusier MK, Amari FL, Bateiha AE, EL-Khateeb MS, Naser AS, *et al*. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. Saudi med J. 2004;25:1046-50.

[13] Flatau E, Trougouboff P, Kaufman N, Reichman N, Luboshhitzky R. Prevalence of hypothyroidism and diabetes mellitus in elderly Kibbutz members. Eur J Epideminol. 2000;16:43-46.

[14] Ditta A, Tayyab M, Qavi A, Malik MA, Chaudhry NA. Significance of thyrotrophin and thyroxine estimations in type 1 diabetes. J Pak Med Assoc. 2001; 51:349-51.

[15] Johnson B. Revealing the cost of type–II diabetes in Europe, Diabetologia. 2002; 45:5-12.

[16] Gursoy N, Tuncel E, Ertrk E, Imamoglu S, Arinik A. The relationship between the glycemic control and the hypothalamus pituitary-thyroid axis in diabetic patients.Turkish J Endocrinol and Metab. 1999;4:163-68.

[17] Suzuki J, Nanno M, Gemma R, Tanaka I,Taminato T, YoshimiT. The mechanism of thyroid hormone abnormalities in patients with diabetes mellitus. Nippon Niabunpi. Gakki Zasshi. 1994;7:465-70.

[18] Celani MF, Bonati ME, Stucci N. Prevalence of abnormal thyrotrophin concentrations measured by a sensitive assay in patients with type 2 diabetes mellitus. Diabetes Res. 1994;27:15-25.

[19] Smithson MJ. Screening for thyroid dysfunction in a community population of diabetic patients. Diabet Med. 1998;15:148-50.

[20] Udiong CEJA, Udoh E, Etukudoh ME. Evaluation of thyroid function in diabetes mellitus in Calabar, Nigeria. Indian J. Clin. Biochem. 2007;22:74-78.

[21] Pasupathi P, Bakthavathsalam G, Saravanan G, Sundaramoorthi R. Screening for thyroid dysfunction in the diabetic/non-diabetic population. Thyroid Science. 2008;3:1-6.

[22] Rajan SK, EzhilarasiA, Sasidharan M. Thyroid dysfunction in patients with type 2 diabetes mellitus. J Assoc Phys India. 2003;51:1229.

[23] Al-Wazzan H, Daban A, Askar R, El-Shazly M. Prevalence and associated factors of thyroid Dysfunction among Type 2 diabetic patients, Kuwait. Bull. Alex. Fac. Med. 2010;46:141-48.

 DOI : 10.35291/2454-9150.2019.0022