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Evaluation of Thyroid Dysfunction Among type 2 diabetic Punjabi Population

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ABSTRACT
Diabetes mellitus (DM) is commonly associated with thyroid dysfunction. The aim of the present study was to evaluate the prevalence of thyroid dysfunction in subjects with type 2 diabetes and the effect of type 2 diabetes mellitus on other bio-chemical variables. In the present study 80 type 2 diabetic subjects and 80 healthy non diabetic subjects were investigated for total triidothyronine (T_3), total thyroxin (T_4), free triidothyronine (FT_3), free thyroxine (FT_4) and thyroid stimulating hormone (TSH), plasma glucose fasting(FPG), glycosylated hemoglobin (HbA1c), serum cholesterol, serum triglycerides, high density lipoprotein(HDL), low density lipoprotein(LDL), very low density lipoprotein(VLDL), blood urea, serum creatinine, SGOT and SGPT. The level of T_3, T_4, FT_3 and FT_4 were significantly lower while the level of TSH was significantly higher in type 2 diabetics as compared to non-diabetics. From the 80 diabetic subjects studied, 30% showed abnormal thyroid hormone levels (23.75% had hypothyroidism and 6.25% had hyperthyroidism). Significantly higher levels of FPG, HbA1c, serum cholesterol, serum triglyceride, LDL, VLDL, blood urea, creatinine, SGOT, SGPT and significantly lower level of HDL was observed in diabetics as compared to non-diabetics subjects. The prevalence of thyroid dysfunction among type 2 diabetic Punjabi population is very high with subclinical hypothyroidism being more common. All patients with type 2 diabetes should undergo bi-annual screening to detect asymptomatic thyroid dysfunction and other bio-chemical variables to improve the quality of life and reduce the morbidity rate.
Keywords : *Diabetes , Hypothyroidism , Hyperthyroidism, T_3,T_4, FT_3, FT_4,TSH*

INTRODUCTION

Diabetes mellitus (DM), a common endocrine metabolic disorder, is a leading cause of death worldwide [1]. It is characterized by hyperglycemia resulting from a variable interaction of hereditary and environmental factors and is due to the combination insulin resistance (impairment in insulin-mediated glucose disposal) and defective secretion of insulin by pancreatic β-cells or both [2]. The WHO estimate of diabetes prevalence for all age groups world wide was 2.8% in 2000 and 4.4% in 2030. The total no. of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030[3]. Factors such as sedentary lifestyle, dietary modifications, ethnicity, hypertension and obesity have led to a dramatic increase in the incidence of diabetes mellitus, especially in the 21st century [4]. Thyroid disorders are also very common in the general population and it is second only to diabetes as the most common condition to affect the endocrine system. As a result it is common for an individual to be affected by both thyroid diseases and diabetes. The first report showing the association between diabetes and thyroid dysfunction were published in 1979 [5,6]. Since then a number of studies have estimated the prevalence of thyroid dysfunction among diabetes patients to be varying from 2.2 to 17 % [7,8]. However, fewer studies have estimated much higher prevalence of thyroid dysfunction in diabetes i.e. 31 % and 46.5% respectively [9, 10].

Thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism and excess and deficit of any one can result in functional derangement of the other [11]. Thyroid disease is a pathological state that adversely affects diabetic control and is commonly found in most forms of DM which is associated with advanced age in type 2 diabetes and autoimmune diseases in type 1diabetes. DM appears to influence thyroid function in two sites; firstly at the level of hypothalamic control of TSH release and secondly at the conversion of T_4 to T_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 level of T_4 [12]. Since

thyroid hormone regulate metabolism and diabetes can alter metabolism of food stuff, the metabolism of organisms may be further affected of the combination of thyroid disease and diabetes.
Till date not much data is available about thyroid diseases in diabetes in the Punjabi population. The aim of the present study was to evaluate the prevalence of thyroid dysfunction in subjects with type 2 diabetes mellitus and also the effect of the type 2 diabetes on other biochemical variables in Punjabi population.

MATERIALS AND METHOD

The subjects were selected from the cases presenting with diabetes mellitus 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 80 type 2 diabetic and 80 non diabetic subjects. The criteria for diagnosis of type 2 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 patients on medications that can affect thyroid function were also 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 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, HbA1c, lipid profile, blood urea, serum creatinine, SGOT, SGPT. 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), HbA1c (normal range 4.2-6.2%), serum cholesterol (normal range150-200 mg/dl), serum triglycerides (normal range 100-150 mg/dl), serum HDL (normal range 35-48 mg/dl), serum LDL (normal range <130), serum VLDL (normal range 5-35 mg/dl), blood urea (normal range 10-45 mg/dl), serum creatnine (normal range 0.5-1.4 mg/dl), SGOT (normal range 5-42 mg/dl) and SGPT (normal range 5-40 mg/dl), 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 $\pm$ SD. The comparison was done by student t test on no. of variable of each parameter using SPSS version 10.

RESULTS AND DISCUSSION

Table 1 presents the sex and age distribution of non-diabetic and diabetic subjects. Both Type 2 diabetic and non diabetic subjects included 36 male and 44 females with mean age of 46.05 ± 4.99 and 46.15 ± 5.13 respectively.

Table 1: Sex and age distribution of non-diabetic and diabetic subjects.

Group	Sex	No.	Mean age in years
Type 2 Diabetic Subjects	Male	36	
(N= 80)	Female	44	46.05±4.99
Non Diabetic Subjects	Male	36	
(N=80)	Female	44	46.15±5.13

Table 2 shows the levels of various laboratory parameters in diabetic and non-diabetic subjects. FPG, HbA1c, serum cholesterol, serum triglycerides, serum LDL, serum VLDL, SGOT, SGPT, serum creatinine and blood urea were significantly higher in diabetic subjects as compared to non-diabetic subjects while serum HDL was significantly lower in diabetic as compared to non-diabetic subjects.

Table 2: Comparison of various Biochemical Parameters in Type 2 Diabetic and Non Diabetic control groups

Investigations	TYPE 2 Diabetes mellitus N = 80 Mean ± SD	Non Diabetic Control Group N = 80 Mean ± SD	p Value
Serum Cholesterol (mg/dl)	191.57 ± 29.64	167.63 ± 9.03	<0.0001
Serum Triglycerides(mg/dl)	163.20 ± 34.92	126.01 ± 15.51	<0.0001
Serum HDL (mg/dl)	43.4 ± 4.88	44.78 ± 1.40	0.0162
Serum LDL (mg/dl)	115.09 ± 25.48	97.64 ± 7.22	<0.0001
Serum VLDL(mg/dl)	33.64 ± 7.02	25.21 ± 3.11	<0.0001
SGOT(U/L)	34.7 ± 7.61	30.03 ± 3.80	<0.0001
SGPT((U/L)	37.2 ± 7.93	32.39 ± 3.65	<0.0001
Blood Urea(mg/dl)	35.5 ± 6.15	30.11 ± 2.05	<0.0001
Serum Creatinine (mg/dl)	1.2 ± 0.2	1.00 ± 0.07	<0.0001
FPG (mg/dl)	159.0 ± 14.51	89.45 ± 6.58	<0.0001
HbA1c (% age)	7.22 ± 0.77	5.04 ± 0.20	<0.0001

Diabetes has a profound impact on life expectancy. A person diagnosed with type 2 diabetes mellitus in middle age (40-60 years) stand to lose as much as 10 years of life expectancy. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart, liver, blood vassals and other endocrine organs.

In this study diabetic subjects show significant higher serum levels of cholesterol, triglycerides, LDL, VLDL and lower level of HDL as compared to non diabetic subjects. Our results are in consistence with previous cross sectional study conducted among young adult population by Sawant *et al*., [13] where increase prevalence of dyslipedemia was found to be the major contributor of CVD. The abnormally high concentration of serum lipid in diabetes is mainly due to the increase in mobilization of free fatty acids from peripheral fat depots [14]. Insulin resistance, an important factor in type 2 diabetes mellitus, leads to excessive liberation of free fatty acids from adipose tissue, [15,16] which activates the signaling enzyme protein kinase C, inhibits phosphatidylinositol-3 (PI-3) kinase (an eNOS agonist pathway), and increase the production of reactive oxygen species. This mechanism directly impairs nitric oxide (NO) production or decreases its bioavailability once produced [17]. Monocytes, upon reaching the subendothelial space, internalize oxidized low-density lipoprotein cholesterol (LDL-c) via scavenger receptors and become foam cells. Localized accumulation of foam cells leads to formation of fatty streaks, the hallmark of early atherosclerotic lesions [18]. There was also significant increase in blood urea and serum creatinine in diabetic patients compare to non diabetic controls subjects. The above results corresponded with the finding of Mittal et al. [19] having mean values for serum creatinine (1.13 ± 0.20 mg/dl) were increased in diabetic subject with no kidney diseases as compared to normal subjects (1.03 ± 0.07 mg/dl). This is

because high blood sugar level in diabetes damage millions of nephrons which are tiny filtering units with in each kidney with time. As a result, kidneys are unable to maintain the fluid and electrolyte homeostasis. Creatinine is filtered by the glomerulus, therefore, serum creatinine level is used as an indirect measure of glomerular filtration. As glomerular filtration rate (GFR) diminishes, there is a rise in plasma concentration of serum creatinine and urea. Hyperglycemia is a precondition for developing two major early glomerular lesions, glomerular basement membrane (GBM) thickening and mesangial expansion, which are not present at the diagnosis of diabetes but are found 2 to 5 yrs after onset of hyperglycemia [20]. In chronic hyperglycemia, there is non enzymatic glycation/oxidation of amino acids, lipid and lipoproteins. The formation of advanced glycation end-products (AGEs) has long been recognized as a fundamental mechanism of cellular injury in diabetes. The accumulation of AGEs accelerates atherogenesis, increased vascular permeability, basement membrane thickening, increased extracellular matrix and mesangial fibrosis. This process leads the way to eventual glomerulosclerosis and renal failure [21]. There was also significant increase in SGOT and SGPT in type 2 diabetic patients as compare to non diabetic controls. These results are in accordance with the findings of Idris et al, [22] who found that the levels of SGOT and SGPT in type 2 Sudanese diabetic patients were significantly higher as compared to non diabetic controls.

Table 3 shows the level of serum thyroid hormones in diabetic and non-diabetic subjects. The serum levels of Free T_3, Free T_4, T_3 and T_4 were significantly lower in diabetic subjects as compared to non-diabetic subjects while level of serum TSH was significantly higher in diabetic subjects as compare to non-diabetic subjects

Table 3: Comparison of Thyroid Function Test in Type 2 Diabetic and Non Diabetic control groups

Investigations	TYPE 2 Diabetes mellitus N = 80 Mean ± SD	Non Diabetic Control Group N = 80 Mean ± SD	p Value
Serum Free T_3 (pg/ml)	2.24 ± 0.87	2.88 ± 0.33	<.0001
Serum Free T_4 (ng/dl)	1.07 ± 0.44	1.24 ± 0.11	0.001
Serum T_3 (ng/dl)	119.7 ± 42.19	144.14 ± 13.48	<0.0001
Serum T_4 (ug/dl)	7.15± 2.17	8.07 ± 0.79	0.0005
Serum TSH (uIU/ml)	5.63 ± 5.34	2.31 ± 1.62	<0.0001

Table 4 and figure 1 shows the distribution of thyroid disorder according to the gender in type 2 diabetes mellitus and non diabetic control subjects. Out of 80 type 2 diabetic subjects studied, 30% shows abnormal thyroid functions (23.75% had low thyroid hormone level and 6.25% had high thyroid hormone level) and 70% shows normal thyroid hormone level as shown in fig.2. The incidence of hypothyroidism was more in females as compare to males in type 2 diabetes.

Table 4: Type of thyroid disorders according to gender in type 2 diabetes mellitus and non diabetic control group

Distribution of Subjects according to gender	Types of Thyroid disorders			
	Subclinical Hypothyroidism	Primary Hypothyroidism	Subclinical Hyperthyroidism	Primary Hyperthyroidism
Type 2 Male	**4**	**2**	**0**	**2**

DM (N=80)	**Female**	**8**	**5**	**0**	**3**
	Male	**1**	**0**	**0**	**0**
Non Diabetic (N=80)	**Female**	**2**	**0**	**0**	**0**

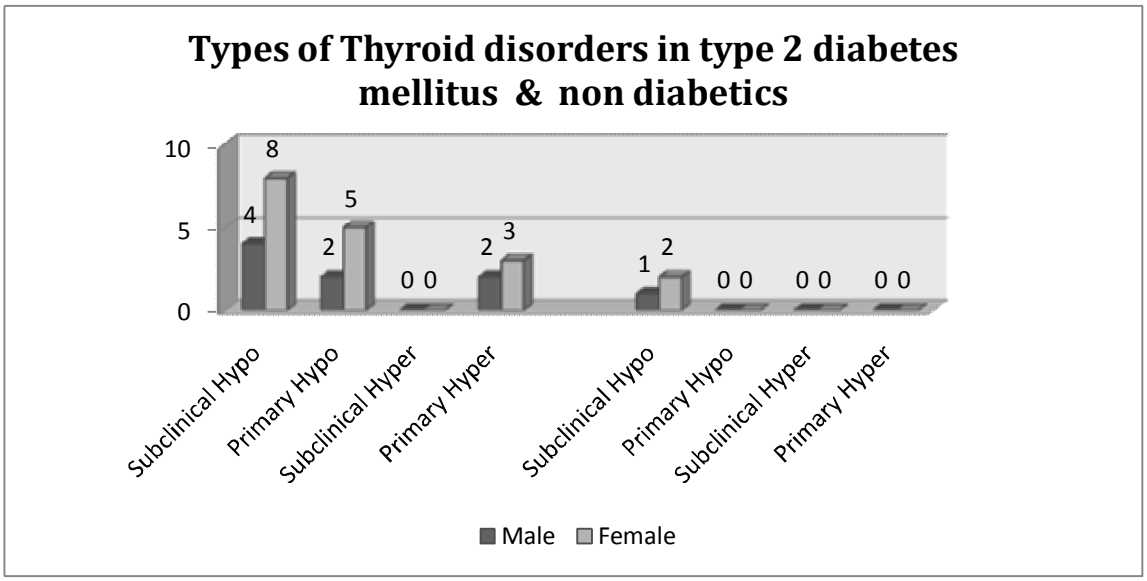

Fig 1. The distribution of thyroid disorder according to the gender in type 2 diabetes mellitus and non diabetic control subjects

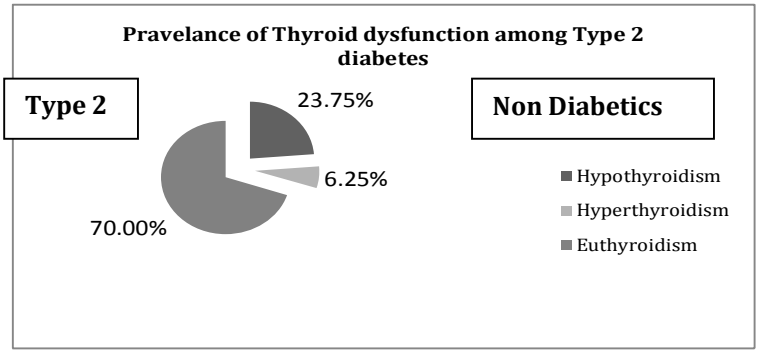

Figure 2

The present study reported high incidence of abnormal thyroid hormone level in type 2 diabetic population. Our observation is in agreement with reports of Suzuki et al, [23]; Celani *et al*, [9] and Udiang *et al*, [10] who in separate studies found altered thyroid hormone level of different magnitude in diabetic patients.

The present study reveals different grades of thyroid dysfunction among diabetes. Hypothyroidism is present in 23.75% (15% subclinical hypothyroidism and 8.75% Primary hypothyroidism) and hyperthyroidism is present in 6.25% (all primary hyperthyroidism) of diabetic subjects. This goes in accordance with the reports of Suzuki *et al,[*23] and Smithson *et al*,[8] who in separate studies found altered thyroid hormone level of different magnitude (both low and high) in diabetic patient. The abnormal thyroid hormone level may be the out come of various medications the diabetes was receiving. For example, it is known that insulin [24], 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 phenylthioureas are known to suppress the level of FT_4 and T_4, while causing raised levels of TSH [25, 26]. Some of the type 2 diabetic was 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 hormones levels in some of the euthyroid diabetics. The presence of both raised and low levels of thyroid hormones levels in diabetics in this study may also be due to modified thyroid releasing hormone(TRH)s synthesis and release[27] and may depend on the glycaemic status of the diabetics studied. Glycaemic status is influenced by insulin, which is known to modulate TRH and TSH levels [28]. Suzuki *et al.* [25] attributed the abnormal thyroid hormone levels found in diabetes to the presence of thyroid hormone binding inhibitor (THBI), an inhibitor of the extra thyroidal conversion enzyme (5'-deiodinase) of T_4 to T_3, and dysfunction of the hypothalamo-pituitary-thyroidaxis. These situations may prevail in diabetes and would be aggravated in poorly controlled diabetics.

CONCLUSION

Thus this study show high incidence of abnormal thyroid hormone level among type 2 diabetic subjects. Failure to recognize the presence of abnormal thyroid hormone level in type 2 diabetes may be a primary cause of poor management often encountered in some treated type 2 diabetics. There is therefore need for the routine assay of thyroid hormones in type 2 diabetic, particularly in those patients whose conditions are difficult to manage.

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