Study on Association of Thyroid Dysfunction with Diabetes Mellitus At Tertiary Care Hospital

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Abstract: *Thyroid disease adversely affects glycemic control in diabetes and it affects the health. In diabetic patients thyroid disorder is commonly found and associated with advanced age in type-2 diabetes.*
Objectives:*To determine association among T_3 ad T_4 ,TSH level in type-2 diabetes with glycemic control.*
Material And Methods:*This study was carried out in department of Biochemistry in association with department of General medicine & Endocrinology of Mahatma Gandhi Medical College & Hospital, Sitapura, Jaipur.100 Clinically diagnosed and biochemically confirmed cases of type-2 DM were studied.*
Statistical analysis:*students 't' test and chi-square test were used for analysis . A p-value of < 0.05 shall be considered as statistically significant.*
Result:*18% of the total subjects were suffering from thyroid disorders. While 13% patients confirmed for hypothyroidism, 5% were found to have hyperthyroidism. The remaining 82% patient exhibited a normal thyroid function.serum T_3, T_4 levels were observed to be significantly low and TSH was higher in the patients with poor glycemic control. (P<0.05S). It was observed that in the good controlled group only 6.7% patients exhibited hypothyroidism while 23% patients of the poor glycemic control group suffered from hypothyroidism (P= 0.003).The prevalence of thyroid disorders increase with age i.e. more than 40 years.*
Keywords:*DM type II, thyroid disorders*

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I. Introduction

In present scenario thyroid diseases and diabetes mellitus (DM) both are the most common endocrine disorders encountered in clinical practice. Interestingly both have shown great association too and an association between both conditions has been reported. A meta-analysis reported a frequency of 11% in thyroid dysfunction in the patients of DM[2]Autoimmunity has been implicatedto be the major cause of thyroid-dysfunction associated DM.According to World Health Organization Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of microvascular damage.It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease), and diminished quality of life.According to the Indian Heart Association 2015, India is the "Diabetic Capital of the World" with a projected109 million individuals with diabetes by 2035.[6].Type-2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy.This is partly due to a number of complications with which it is associated, including: two to four times the risk of cardiovascular disease, including ischemic heart disease and stroke; a 20fold increase in lower limb amputations, and increased rates of hospitalizations.[7]

Various studies have estimated the prevalence of thyroid disorder in diabetic patients [8] In few studies higher prevalence of thyroid dysfunction in diabetes has been estimated [9;10].In diabetic patient thyroid disorder prevalence is higher as compared to general population [11]

Insulin and thyroid hormones are involved in cellular metabolism and thus excess or deficit of either of these hormones result in the functional derangement of the other. The physiological and biochemical interrelationship between insulin and the influence of both insulin and iodothyronines on the metabolism of carbohydrates, proteins and lipids are recorded. Such records indicate that iodothyronines are insulin antagonist with high levels being diabetogenic while absence of the hormone inhibits the development of diabetes [12] The thyroid hormone replacement is associated with a decrease in glycosylated haemoglobin (HbA1C) level, which is influenced by increased erythropoiesis rather than by changes in glucose level [13]. Hyperthyroidism impairs glycemic control in diabetic subjects,while hypothyroidism increases susceptibility to hypoglycemiathus complicating diabetes management.Thyroid disease adversely affects glycemic control in diabetes and it affects the health. In diabetic patients thyroid disorder is commonly found and associated with advanced age in type-2 diabetes [15]

So, through the present study, an attempt is made to assess the association of thyroid profile with glycemic control in patients with type-2 DM patients so the present study was planned with the following objectives

To know the spectrum of thyroid dysfunction in diabetes mellitus.

1. To determine association amongT_3 ad T_4, TSH level in type-2 diabetes with glycemic control.

II. Materials And Methods

Present study was carried out in department of Biochemistry in association with department of General medicine & Endocrinology of Mahatma Gandhi Medical College & Hospital, Sitapura, Jaipur. The study was conducted after seeking approval from institutional ethic committee. 100 Clinically diagnosed and biochemically confirmed cases of type-2 DM were enrolled with age group of upto 60 years either gender, willing to participate and sign consent document and patient willing to comply with the protocol requirement.Patients above 60 years of age, pregnancy, alcoholics, with gross hepatic or renal dysfunction and pulmonary infarction.,with rheumatoid arthritis, Duchenne's muscular dystrophy, polymyositis and other causes for transient increase in CK,Patients on drugs like statins, diuretics, antihypertensives, steroids, etc lithium and amiodarone were excluded from the study

An informed consent was taken from all patients fulfilling the inclusion criteria before the collection of the sample from cases. The study was conducted after approval from the institutional Ethics committee.For Biochemical investigation blood samples of selected patients after overnight fasting of at least 12 hrs. of venous blood was collected by standard aseptic techniques. About 10 ml of blood samples were collected by venipuncture into labeled gel plain vial and a fluoride vial.

*   After collection blood samples were allowed to coagulate after which they were centrifuged at 3000 rpm for 5 minutes to obtain serum.
*   The samples collected shall be subjected to following investigations:

Routine Clinical Investigations: Blood Sugar Fasting and Blood Sugar Postprandial and HbA1C were estimated by colorimetric method on fully automated analyzer VITROS 4600.

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Estimation of Blood Sugar

Glucose is a primary cellular energy source. Fasting plasma glucose concentrations and tolerance to a dose of glucose are used to establish the diagnosis of DM and disorders of carbohydrate metabolism. Glucose measurements are used to monitor therapy in diabetics and in patients with dehydration, coma, hypoglycemia, insulinoma, acidosis, and ketoacidosis.

III. Statistical Analysis

The quantitative variables were presented of mean ± SD. Results were compared by applying students 't' test.The qualitative data were present as number and percentages and were evaluated by applying chi-square . A p-value of < 0.05 shall be considered as statistically significant.

Observations and Results

18% of the total subjects were suffering from thyroid disorders. While 13% patients confirmed for hypothyroidism, 5% were found to have hyperthyroidism. The remaining 82% patient exhibited a normal thyroid function .The patients enrolled for the study were grouped based on the glycemic control that was measured as % HbA1C. HbA1C $\leq 8.0\%$ was considered as good glycemic control (n=30) while HbA1C >8.0% indicated a poor glycemic control (n=70) (Table1).(Table No2)The mean age in the both group (HbA1C $\leq 8.0\%$ & HbA1C > 8.0%) was comparable with no significant difference.Male:Female distribution for the patients enrolled was 60:40. In the sub-group, the ratio was euthyroid male 49 & euthyroid female 33, Hyperthyroidism Male 2 & female 3, Hypothyroidism Male 9 & female 4.On comparing the various parameters among the two groups it was observed that the mean age in both the group was comparable with no significant difference. The fasting & postprandial blood sugar levels were found to be significantly higher in the poor control group .The mean HbA1C level of the good glycemic control group was 6.93 ± 0.72% whereas that of the poor glycemic control group was 10.60 ± 1.71%(P-value = 0.001S) .On comparing the thyroid function test i.e. serum levels of T_3, T_4 and TSH among the two groups, serum T_3 levels were observed to be significantly low in the patients with poor glycemic control (p=0.005) Similarly, the serum T_4 levels were also significantly lower in the poor glycemic control group. However, the fall of serum T_3 levels was more significant as compared to that of serum T_4 levels. (P-value = 0.035).   Serum TSH was also significantly higher in the poor glycemic control group (P-value-0.014). **(Table2)**

Based on the glycemic control and the thyroid status, the subjects were subcategorized as Euglycemic euthyroid 31%, Hyper glycemic euthyroid 51%, Euglycemic hypothyroid 4%, Hyper Euglycemic hypothyroid 9%, Euglycemic hyperthyroid 2%, Hyperglycemic hyperthyroid 3%.It was observed that in the good controlled group only 6.7% patients exhibited hypothyroidism while 23% patients of the poor glycemic control group suffered from hypothyroidism (X^2 = 8.824, P= 0.003).**(Table No2)**

The subjects enrolled for the study were further subcategorized on the basis of the age. Total 100 type-2 Diabetes patients, in this 20% patients were ≤ 40 years of age all these patients were euthyroid.Almost 50% of the total patients were in the age group of 41-60 years. 23.5% of these patients (n=12 out of 51) showed primary hypothyroidism.29 out of 100 diabetic patients were above 60 years of age of those (20.7%) suffered from thyroid disorders.These observations suggest that the prevalence of thyroid disorders increase with age i.e. more than 40 years. **(Table No.3)**

IV.   Discussion

Among the endocrinal metabolic diseases, diabetes is a major concern. The disease is responsible for significant mortality and morbidity due to various complications(Ravishankar SNet. al., 2013).A total of 100 diagnosed patients of type-2DM were enrolled for the study on the basis of pre-defined inclusion & exclusion criteria. On reviewing the thyroid function of the selected patients, it was observed that 18% of the total subjects were suffering from thyroid disorders. While 13% patients confirmed for hypothyroidism, 5% were found to have hyperthyroidism. The remaining 82% patient exhibited a normal thyroid function (Table).In a similar study by Uppal V et. al., 2013 the prevalence of thyroid disorder was reported as 24.5%. The distribution of hypothyroid & hyperthyroid patients was 17%& 7.5% respectively. These findings reflect that almost 1/5th of the diabetic subject suffer from thyroid dysfunction.Similarly, in study by Pasupathi P et. al.,2009,it was found that prevalence of thyroid disorder was 45% among type-2 diabetics. Hypothyroidism was present in28% and 17% had hyperthyroidism.Perros P et. al., 1995 demonstrated an over-all prevalence of 13.4% of thyroid diseases in diabetics with the highest prevalence in type -1 diabetics female (31.4%) and lowest prevalence in type-2 male diabetics(6.9%).Vikram BV et. al., 2013 also reported high prevalence of thyroid disorders in type-2 DM. Hypothyroidism was present in 22% (14% subclinical hypothyroidism and 8% primary hypothyroidism) and hyperthyroidism is present in 8% (all primary hyperthyroid subjects) of diabetic subjects.

The patients enrolled for the study were grouped based on the glycemic control that was measured as % HbA1C. HbA1C ≤ 8.0% was considered as good glycemic control (n=30) while HbA1C >8.0% indicated a poor glycemic control (n=70) (Table2; Figure 2).The high percentage of patients with poor glycemic control was alarming and needs thorough review and analysis.On comparing the various parameters among the two groups it was observed that the mean age in both the group was comparable.The mean HbA1C level of the good glycemic control group was significantly lower than the poor glycemic control group.On comparing the thyroid function test ,serum $T_{3 \text{ and } T4}$ levels were observed to be significantly low in the patients with poor glycemic control (p=0.005). However, the fall of serum T_3 levels was more significant as compared to that of serum T_4 levels. (Table2)Low serum T_3 is probably due to reduced peripheral conversion of T_4 to T_3 via 5′ monodeiodination reaction (Schlienger JL et.al., 1982).Diabetes and thyroid disorders have been reported to influence each other (Hage M et. al., 2011).

Insulin and thyroid hormones are both involved in cellular metabolism. Excessive deficiency of either of these two hormones affects the functioning of other. Boththese hormones have been reported to affect the metabolism of carbohydrate, protein & lipid(Uppal Vibha et. al., 2013)[17]. Previous studies have also reported iodothyroninesto be antagonist of insulin (Granner DK et. al., 2000)[12]. Kim MK et. al.(2010)[13]have suggested that decreased HbA1c is associated with thyroid hormone replacement. On the other hand, excessive thyroid hormones increase insulin resistance as well as degradation.In a recent research, Suresh DR et. al., (2014)[21] have recommended that early detection of abnormal thyroid hormone level in sub-clinical thyroid patient with type-2DM can be helpful in better management of patients and prevention of complications (Granner DK et. al., 2000)[12].Insulin plays a key role in cellular uptake of glucose from plasma. In type 1 diabetes, insulin is absolutely deficient & relatively deficient in type-2 diabetes. Raised levels of free circulatory serum T_3&serum T_4 leads to hyperglycemia due to several factors like polyphagia, increased glycogenolysis and stimulating degradation of insulin. On the contrary, reduced thyroid hormones level i.e. hypothyroidism may cause hypoglycemia (Rochon C et. al., 2003) [22].

Thyroid hormones directly control insulin secretion. In hypothyroidism, there is a reduction in glucose-induced insulin secretion by beta cells, and the response of beta cells to glucose or catecholamine is increased in hypothyroidism due to increased beta cell mass. Moreover, insulin clearance is increased in thyrotoxicosis**(Mitrou P et. al., 2010)[23].**

Type-2 diabetic patients with thyroid dysfunction have been proven to be more susceptible to ketosis (**Beylot M et. al., 1980**)[24]and ketogenesis (**Beylot M,1996**)[25]. Insulin resistance has been shown to be associated with sub clinical hypothyroidism, which is in turn linked to impaired lipid balance and risk of development of metabolic syndrome(**Wang CC et. al., 2012**)[26].

Based on the glycemic control and thyroid states the subjects were categorized as Euglycemic euthyroid 31%,Hyperglycemic euthyroid 51%,Euglycemic hypothyroid 4%,Hyperglycemic hypothyroid 9%,Euglycemichyperthyroid 2% and Hyperglycemichyperthyroid 3% (Table3; Figure 1) The interrelationship between DM and thyroid disorders involves various complex biochemical, genetic, hormonal and pathophysiological mechanism under the influence of endocrine and non-endocrine organs.5- adenosinemonophosphate activated protein kinase is a central target for modulation of insulin sensitivity and feedback of thyroid hormones. The hyperglycemia observed in type-2 DMhas a negative effect on thyroid function. It causes blunting of the pituitary TSH response to stimulation by hypothalamic TRH(**Suresh DR et. al., 2014**)[21]. The probable mechanism is the alteration of TRH activity due to post-translational glycosylation. It also influences the conversion of T_4 toT_3 in the peripheral tissue(**Duntas LH et. al., 2011**)[27].

To explore the influence of glycemic control on thyroid function, chi square test was applied.It was observed that in the good controlled group only 6.7% patients exhibited hypothyroidism while 23% patients of the poor glycemic control group suffered from hypothyroidism(X^2=8.824; P=0.003). This finding confirms that poor glycemic control affects thyroid function and increases the prevalence of hypothyroidism.In the present study the male : female ratio was 60:40%.Of the total females 10% suffered from hypothyroidism. On the other hand, 9 out of 60 males i.e. 15% suffered from hypothyroidism.
The overall prevalence of thyroid disorder was 18.3% in male and slightly lower 17.5% in females.

Several studies have tried to evaluate the prevalence of thyroid disease in type-2 diabetes mellitus on the basis of gender. In a study by (**Ravishankar SNet. al., 2013**)[16], females had high incidence of thyroid disease (36%) as compared to 22% in males.**Perros P et. al.(1995)**[8] demonstrated an overall prevalence of 13.4% ofthyroid diseases in diabetics with the highest prevalence in type-1female diabetics (31.4%) and lowest prevalence in type-2 male diabetics (6.9%).The subjects enrolled for the study were further subcategorized on the basis of age.Of the total 100 type-2diabetes patients, 20% were ≤ 40 years of age.This subcategory showedno case of thyroid dysfunction.51 of the patients were in the age group of 41-60 years i.e. almost 50% of the total enrolled patients. 23.5% of the patients of this group (n=12 out of 51) showed thyroid dysfunction primarily hypothyroidism. The third sub category included patients >60 years of age (n=29), 6 patients (20.7%) of this age group suffered from thyroid disorders.The above observations suggest that the prevalence of thyroid disorders increases with age i.e. more than 40 years.

In the study by **Ravishankar SNet. al., 2013,**[16]it was observed that the thyroid disorder specially hypothyroidism is more common in the higher age group in diabetic patients.In a recent study by **Khurana A et. al., 2016**[28]the overall prevalence of thyroid disease in type-2diabetes was 16% that is very close to the present study i.e.18%.This study also found that the prevalence is higher in females, higher age and patients with uncontrolled diabetes.The present study therefore, undertaken to strongly recommends the need of determination of thyroid dysfunction in the patients of type-2DM. Testing for thyroid dysfunction in type-2DM patient is necessary and should be carried out annually.The American Thyroid Association guidelines for type-2DM patients require frequent testing from 35 years of age, and every 5 years thereafter in adults (**Perros P et. al., 1995**)[8].Regular screening will be helpful for detection of thyroid abnormalities in all diabetic patients and will allow early treatment of subclinical thyroid dysfunction.The present study also confirms that there is a high incidence of thyroid disorders in type-2DM which is further higher in age above 40 years and in poor glycemic control.The study further recommends research for evolution of influence of thyroid dysfunction on risk marker of diabetes associated complication. The study of thyroid functions with markers of endothelial functions and microvascular damage should also be interesting to explore.

V.   Conclusion

It has been repeatedly proven that the association between thyroid dysfunction and DM is evident.Presence of abnormal thyroid hormone levels in diabetics, if unrecognized, may be a primary cause of poor management. So there is need for the routine assay of thyroid hormones in diabetics which will help in the early detection of any deviation, it will alsobe helpful in improving the treatment of thyroid dysfunction as well as overall reduction of morbidity & mortality.Further studies on association of thyroid dysfunction with markers ofCardiovascular disease(CVD), endothelial dysfunction and other complications of type-2 diabetes are recommended.

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Table 1: Distribution of patients on the basis of thyroid function

	Euthyroid(N=82)	Hyperthyroidism (N=5)	Hypothyroidism (N=13)	P Value LS
Age (Years) ☐ 40	20(24.4)	0(0)	0(0)	0.18NS
41-60	39(47.6)	4(80)	8(61.5)	
>60	23(28)	1(20)	5(38.5)	
Male	49(59.75)	2(40)	9(69.23)	0.53NS
Female	33(40.24)	3(60)	4(30.76)	

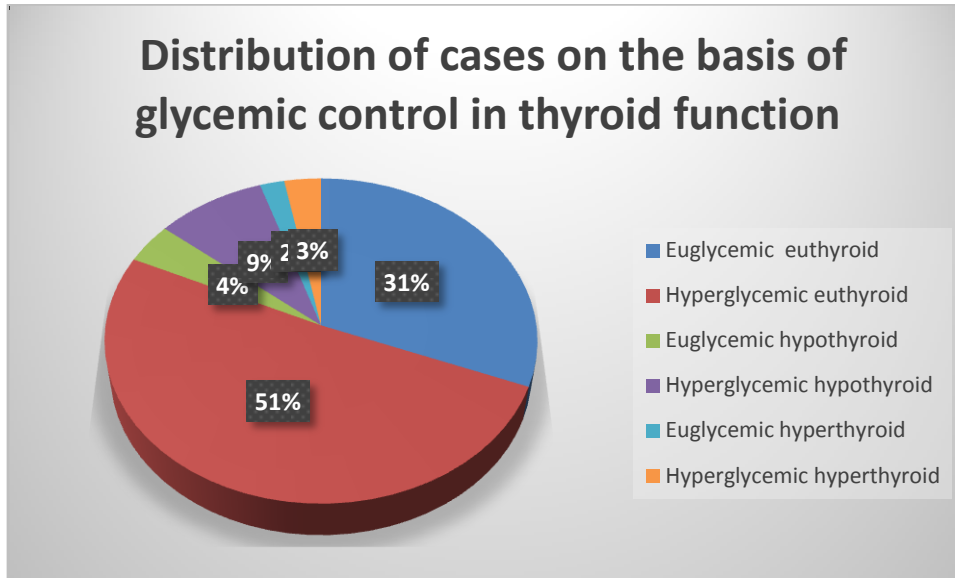**Table No 2:** Distribution of Blood investigation in the groups based on the glycemic control

Group	HbA1C ☐ 8.0	HbA1C > 8.0	P-Value
No. of cases (n)	30	70	
Age (Years)	53.23 ± 12.34	52.21 ± 12.39	>0.05NS
BSF (mg/dl)	139.6 ± 62.64	220.21 ± 75.75	<0.001S
Blood Sugar PP (mg/dl)	164.0 ± 63.62	377.29 ± 146.36	<0.001S
HbA1C %	6.93 ± 0.72	10.60 ± 1.71	<0.001S
T_3 (ng/ml)	1.55 ± 0.78	1.21 ± 0.28	0.005
T_4 (µg/dl)	9.20 ± 3.09	8.17 ± 2.05	0.035
TSH (µIU/ml)	1.99 ± 1.53	3.21 ± 2.46	0.014

TSH ≤4.68	28(93.3)	16(23)	0.003
TSH >4.68	2(6.7)	54(77)	

Table3: Distribution of cases on the basis of glycemic control in thyroid function

	Euthyroid	Hyperthyroidism	Hypothyroidism	Total
Euglycemic	31	4	2	37
Hyperglycemic	51	9	3	63
	82	13	5	100

Chi-square =   0.259 with 2 degrees of freedom;   P = 0.879NS