



Original Research Article

Correlation of T₃, T₄, TSH with fasting plasma glucose and glycosylated haemoglobin in patients of type 2 diabetes mellitus

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ABSTRACT

The two most common endocrine disorders encountered in clinical practice are Thyroid diseases and Diabetes Mellitus. Diabetes and thyroid disorders have been shown to reciprocally influence each other and an association between both conditions are generally reported. Thyroid disease is a hazardous condition as it can lead to uncontrolled glycemic control in diabetic patients. Thyroid disease is found usually in diabetes and is associated with advanced age, particularly in type 2 diabetes. The aim of the present study was to correlate Fasting plasma glucose (FPG) with Thyroid hormones levels and to correlate Glycosylated Hemoglobin levels (HbA_{1c}) with thyroid hormones. The present hospital - based cross sectional study was conducted on sample size of 200 subjects of age more than 40 years. These subjects were divided into two groups- 100 known Type 2 Diabetes Mellitus constituting study group and 100 healthy age and gender matched individuals constituting control group. The thyroid hormones were analyzed with the ELISA method and HbA_{1c} was analyzed using Ion Exchange Resin Method. The results of the present study showed a positive correlation between TSH and FPG, HbA_{1c} with TSH, a negative correlation of HbA_{1c} with T₃ and there was a negative correlation between FPG and T₃.

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1. Introduction

The two most common endocrine disorders encountered in clinical practice all the time are Diabetes mellitus (DM) and thyroid dysfunction (TD).¹ Thyroid hormones are found to influence approximately all the metabolic pathways including carbohydrate metabolism. In contrast, in Type 2 DM, there are inconsistent and variable degrees of insulin resistance (IR) and/or impaired insulin secretion and increased glucose production.^{2,3}

Diabetes Mellitus plays a vital role in influencing the functioning of thyroid function, firstly at the level of hypothalamus by controlling the release of TSH Hypothalamic control. This leads to variations in the HPT axis. The results show a decreased secretion of pituitary TSH, decreased Hypothalamic TRH, and reduced TSH

response to TRH. The second influence of Diabetes is seen at peripheral tissue by converting T₄ to T₃. A fall in the hepatic concentration of T₄-5-deiodinase is seen as a result of hyperglycemia. It is accompanied by low serum concentration of serum T₃ and raised level of reverseT₃ and low, normal and high level of T₄. Therefore it is clear indicator that thyroid hormones control metabolism and diabetes play significant role in altering metabolism.³

Both Thyroid hormones and Insulin are twin controllers for cellular metabolism antagonistically. Therefore, imbalance of any one of them might result in metabolic derangement.⁴

The biochemical and physiological correlation between insulin and influence of both insulin and iodothyronines on the metabolism of carbohydrates, proteins and lipids are documented. The results indicated that iodothyronines are insulin antagonist with high levels being diabetogenic while

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nonexistence of the hormones restrains the development of diabetes.⁵ Glycated hemoglobin (HbA1C) has been an important marker of long term glycemic control which may get altered due to altered thyroid status possibly caused by changes in RBC turnover.⁶ Decreased in glycosylated haemoglobin (HbA1c) level is associated with the thyroid hormone replacement, which is influenced by increased erythropoiesis rather than by changes in glucose level.⁷

Thyroid hormones have an effect on glucose metabolism via quite a few mechanisms. Hypothyroidism is one of the most common type of thyroid dysfunction seen generally in patients with diabetes. This result in reduced hepatic glucose production, which in turn means a reduced insulin dose is required by a diabetic patient with hypothyroidism. Apart from that it has been observed that impaired insulin stimulated glucose utilization occurs, in peripheral tissues in both clinical and subclinical hypothyroidism, which in turn, results in insulin resistance. Thus, hypothyroidism predisposes to hypoglycemia, and at the same time, also causes insulin resistance.⁸ Insulin resistance has been shown to be associated with subclinical hypothyroidism, which in turn is associated to impaired lipid balance and risk of development of metabolic syndrome.⁹

2. Aims and Objectives

1. To correlate T₃, T₄, TSH with fasting plasma glucose levels in diagnosed Type 2 Diabetes Mellitus individuals and control group.
2. To correlate T₃, T₄, TSH with glycosylated Hb levels (HbA_{1C}) in diagnosed Type 2 Diabetes Mellitus individuals and control group.

3. Materials and Methods

The current hospital-based cross-sectional study was conducted on a sample size of 200 subjects who were aged above 40 at the time of the research. They were separated into two groups:

1. 100 diagnosed Type 2 Diabetes Mellitus constituting study group, and
2. 100 healthy age and gender matched individuals constituting control group.

This study had been approved by Institutional Ethical Committee of the Government Medical Committee, Patiala. The patients were informed about the objectives of the study and consent was taken from all the participants. The thyroid hormones Levels were analyzed with the ELISA method and HbA_{1C} was analyzed using Ion Exchange Resin Method.

3.1. Inclusion criteria

1. Individuals having Fasting Plasma Glucose (FPG) more than 126 mg/dl at more than two subsequent

occasions.

2. Individuals who were confirmed diabetics and were on anti-diabetic treatment such as insulin or oral hypoglycemic agents.
3. Those who had consented for the study.

3.2. Exclusion criteria

1. Individuals who were having complications of diabetes mellitus.
2. Individuals who were having any history of thyroid dysfunction (total / subtotal thyroidectomy, lithium, anti thyroid drugs, or Graves disease, carcinoma patients, radiation exposure, toxic multinodular goiter, toxic adenoma and gestational hyperthyroidism).
3. Individuals who did not give their consent.

3.3. Statistical analysis

The data was analyzed using Microsoft Excel Software 2017; SPSS 19.0 version. Chi-Square tests, T- tests and Pearson's Correlation tests were done to analyze the data.

4. Results

There were 200 subjects of age more than 40 years. These subjects were separated into two groups - 100 subjects of known Type 2 Diabetes Mellitus constituting study group and 100 subjects of healthy, age and gender matched individuals comprising control group.

The mean range of age in Non Diabetic patients was 57.7 ± 9.0 in males and 54.7 ± 8.4 in female, Similarly among the Diabetic patients mean age range was 56.0 ± 9.74 in male patients and 56.2 ± 9.55 in female patients and was found statistically highly significant ($p < 0.0001$). It was observed that diabetes was associated with advanced age, predominantly in type 2 diabetes.

The Figure 1 shows that among 100 cases studied 59% have normal level of thyroid hormones, 5% have high levels of thyroid hormones (Hyperthyroidism) and 36% have low levels of thyroid hormones (Hypothyroidism)

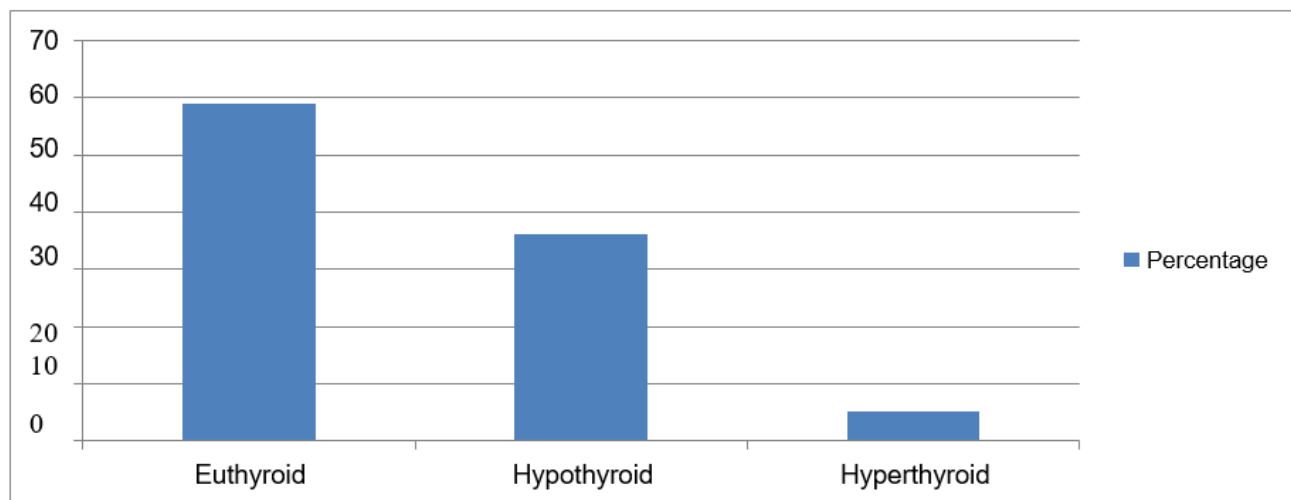
FPG was suggestively higher in type 2 diabetes mellitus subjects as contrast with the non-diabetic subjects ($p < 0.0001$). The serum levels of total T₃ and T₄ were lower in type 2 diabetes mellitus subjects as compared to the controls while the levels of serum TSH were higher in type 2 diabetes mellitus subjects as compared to the controls. All the results were extremely significant statistically ($p < 0.0001$).

Pearson's relationship was attained between FPG and thyroid profile. TSH showed a positive correlation with FPG while there was a negative correlation between FPG and T₃ which is statistically significant ($p < 0.05$). Also there was a negative correlation between FPG and T₄ which was statistically non significant ($p = 0.053$).

Subject's co-relation was calculated between HbA_{1C} and thyroid profile, where TSH showed a positive co- relation

Table 1: Age and sex distribution of diabetic and non diabetic subjects

S.No.	Group	Gender	Number	Age Range Mean $\pm$ SD Range in Years (41-75 years)	p Value
1.	Diabetic Subjects	Male	42	56.0 $\pm$ 9.74	< 0.0001
		Female	58	56.2 $\pm$ 9.55	
2.	Non Diabetic Subjects	Male	38	57.7 $\pm$ 9.0	< 0.0001
		Female	62	54.7 $\pm$ 8.4	

**Fig. 1:** Prevalence of thyroid dysfunction among diabetic patients (n=100)**Table 2:** Comparison of mean of analyzed parameters in diabetic and non diabetic patients

S.No.	Parameter	Normal Range	Cases(Mean + SD)	Controls(Mean + SD)	p Value
1.	T ₃	0.5-1.85 ng/ml	0.71 $\pm$ 0.35	0.99 $\pm$ 0.37	< 0.0001
2.	T ₄	4.8-11.6 μ g/dl	6.43 $\pm$ 3.58	8.66 $\pm$ 5.16	0.0004
3.	TSH	0.4-4.2 UI μ /ml	5.14 $\pm$ 1.53	3.80 $\pm$ 2.72	< 0.0001
4.	FBG	74-100 mg/dl	210.7 $\pm$ 74.4	95.2 $\pm$ 12.9	< 0.0001
5.	HbA ₁ C		7.5 $\pm$ 0.5	5.6 $\pm$ 0.4	< 0.0001

Table 3: Pearson's correlation between FPG and thyroid parameters in diabetic patients

S.No.	Relationship Between	r value	Diabetic Patients p value	Significance
1.	FPG V T ₃	-0.223	0.025	
2.	FPG V T ₄	- 0.194	0.053	
3.	FPG V TSH	0.252	0.011	

Table 4: Pearson's correlation between HbA₁C and thyroid parameters in diabetic patients

S.No.	Relationship Between	r value	Diabetic Patients p value	Significance
1.	HbA ₁ C Vs T ₃	-0.305	0.002	
2.	HbA ₁ C Vs T ₄	0.094	0.350	
3.	HbA ₁ C Vs TSH	0.493	<0.001	HS

with HbA_{1c} which was highly significant. A negative correlation between HbA_{1c} and T₃ was observed and the study was statistically significant. ($p < 0.05$). A positive correlation between HbA_{1c} and T₄ was observed and the study was statistically non-significant ($p = 0.350$).

5. Discussion

Diabetes mellitus is a complex and multifaceted disease which depends on many factors. There could be numerous patho-physiological changes in multiple organ systems caused by the metabolic dysregulation associated with diabetes that impose a heavy burden of morbidity and mortality from macrovascular and microvascular complications of diabetes.¹⁰

Alteration of thyroid hormone levels in diabetic patients are mostly due to modified TRH synthesis and its release. In Type 2 diabetics due to change in post translational glycosylation of TRH this effects biological activities.¹¹

Hyperglycemia is acknowledged to have negative effect on thyroid function thus blunting the pituitary TSH reaction to stimulation by hypothalamic TRH.¹¹

Thyroid dysfunction is also associated with advancing age as there is higher prevalence in elderly women as compared to elderly men. Higher prevalence is observed in diabetic subjects compared to the non-diabetic ones. It is observed in this study that women were more prone to diabetes and there also existed a relationship with advancing age. Non Diabetic patients were 57.7 ± 9.0 in males and 54.7 ± 8.4 in female, Similarly among the Diabetic patients mean age range was 56.2 ± 9.55 in female patients and 56.0 ± 9.74 in male patients which is statistically extremely noteworthy ($p < 0.0001$). It was observed that diabetes was associated with advanced age, particularly in type 2 diabetes.

According to morphological studies, thyroid epithelium undergoes degenerative processes that lead to its flattening; the size of thyroid follicles diminishes, while fibrous connective tissue and lymphoid tissue proliferates. In consequence, the size of the thyroid gland may decrease over a time period and also the ability of the thyroid gland to uptake iodine decreases.¹² Ageing has been proposed to represent a trigger for the progress of autoimmune phenomena consequential in the production of both organ- and non-organ- specific antibodies. Studies on the relationship between sex and thyroid autoimmunity in elderly subjects have shown that the age-related prevalence of antithyroid autoantibodies is greater in women >60 yr of age.¹³

The result of the present study is similar to the study conducted by Elmenshawi I,¹ Małgorzata¹² and Raghuwanshi K et al.¹⁴

The present study shows that among 100 cases studied 59% had normal level of thyroid hormones, 5% had high levels of thyroid hormones (Hyperthyroidism) and 36% had

low levels of thyroid hormones (Hypothyroidism). In cases of hypothyroidism there is decrease in glucose absorption from gastrointestinal tract along with increased glucose accumulation and decreased disposal of glucose leads to hyperglycemia.¹⁵ The present study was similar to the study conducted by Taksali R et al,¹⁶ Raghuwanshi K et al.¹⁴

The present study showed an highly significant ($p < 0.0001$) increase level of TSH in the study group and it also had a positive correlation with both FBG and HbA_{1c}. This may be because of multiple causes like raised Insulin levels raises T₄ level and suppresses T₃ level by inhibiting hepatic conversion of T₄ to T₃. Another reason may be due to autoimmune diseases and due to the presence of thyroid antibodies in patients with DM. The presence of thyroid hormone binding inhibitor (inhibitor of T₄ to T₃ conversion), can be another cause for the dysfunction in hypothalamopituitary thyroid axis and the impact of poor control of diabetes on thyroid hormone concentration.¹

T₃ level has a statistically significant with negative correlation with an increased FPG while T₄ has a non statistically significant negative correlation with increased FPG. This is because Insulin is an anabolic hormone results in inhibition of the hepatic conversion of T₄ to T₃, causes increases the levels of FT₄ while it decreases the levels of T₃.¹⁷

The initial and the most common changes that occur are; reduction in the serum concentrations of total and free T₃, sometimes to extremely low concentrations and secondly, an elevation in the serum concentrations of rT₃ (the low T₃ state). These changes have been ascribed to a block in the 5'- deiodinases with the aim of converting T₄ to T₃ in peripheral tissues.¹⁸ A Similar results were observed in the study conducted by Raghuwanshi K et al.¹⁴ The study shows a affirmative co-relation between HbA_{1c} and TSH and it was highly statistically significant and negative correlation between HbA_{1c} and T₃ which was statistically significant and positive correlation between HbA_{1c} and T₄ and was statistically non significant. Altered glucose homeostasis with reduced absorption and decreased utilization of glucose are related with hyper insulinemia and insulin resistance probably causing transient elevations in the glucose concentrations consequently contributing to glycation of serum protein which was observed by Asmabi et al and Tarig et al.^{17,19}

6. Conclusion

Thus it can be concluded that Triiodothyronine levels are significantly low while TSH levels are increased in patients of type 2 diabetes mellitus when we compare them to non diabetic patients.

Hypothyroidism is frequently observed and most commonly seen in female patients. There was a statistically significant affirmative co-relation between FPG and TSH while a statistically significant negative correlation was

observed between FPG and T_3 and statistically non significant negative correlation between FPG and T_4 . HbA_{1C} has highly significant positive correlation with TSH and statistically significant negative correlation with T_3 . Hypothyroidism may increase the risk of cardiovascular disease in diabetic patients though interrelationships with dyslipidemia, insulin resistance and vascular endothelial dysfunction. Hence it is important for screening of thyroid abnormalities in all diabetic patients.

7. Source of Funding

None.

8. Conflict of Interest

None.

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