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Research Article

EFFECT OF THYROID DYSFUNCTION ON METABOLIC RESPONSE IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Background: Diabetes and thyroid disorders are common disorders of endocrine system in the world. Occurrence of both disorders is also common. Alteration in thyroid hormone levels can affect body metabolism, glycemic control and insulin sensitivity in diabetic patients. So the study is required to find association between various parameters among patients with thyroid disorders and diabetes.
Objective: To find out the prevalence of thyroid dysfunction in type 2 diabetic patients and to evaluate association between thyroid dysfunction, Fasting serum glucose, glycosylated hemoglobin and lipid profile in type 2 diabetic patients.
Materials and Methods: A 100 type 2 diabetic patients were selected for this study. The parameters measured were fasting serum glucose (FSG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), triacylglycerol (TAG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C).
Results: Among the 100 type 2 diabetic patients studied, 32% of the patients have abnormal thyroid hormone levels and 68% have normal thyroid hormone levels. Among the 32% of diabetic patients with abnormal thyroid hormone levels, 22% of them have hypothyroidism (8% clinical hypothyroidism, 14% subclinical hypothyroidism) and 10% of patients have hyperthyroidism (4% clinical hyperthyroidism, 6% subclinical hyperthyroidism). The levels of FSG, HbA1c, TC, TAG, LDL-C are increased significantly ($p< 0.001$) in diabetic patients with thyroid dysfunction when compared with euthyroid diabetics, whereas HDL-C levels are decreased significantly ($p<0.001$) in diabetic patients with thyroid dysfunction than euthyroid diabetics.
Conclusion: Our findings suggest that screening of thyroid dysfunction in type 2 diabetic patients is necessary because thyroid dysfunction when associated with diabetes can produce significant metabolic disturbances.
Keywords: Type 2 diabetes mellitus, Thyroid dysfunction, Dyslipidemia, Glycosylated hemoglobin, Total cholesterol, Triacylglycerol, Low density Lipoprotein-cholesterol, High density lipoprotein-cholesterol

INTRODUCTION

Diabetes mellitus is an important health problem affecting major population worldwide. It is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action associated with chronic hyperglycemia and disturbances of carbohydrate, lipid, and protein metabolism[1].

The WHO estimate of diabetes prevalence for all age groups worldwide was 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030[2]. 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[3]. India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world"[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[5]. A number of studies have estimated the prevalence of thyroid dysfunction among diabetic patients to be varying from 2.2 to 17 %[6,7]. However, recent studies have estimated much higher prevalence of thyroid dysfunction in diabetes i.e. 24%, 30%, 43%, 45%, and 46.5% respectively of these studies[8,5,9,1,10].

Lipid disorders are common in diabetes mellitus, and play crucial roles in the development of diabetic cardiovascular complications. Diabetic dyslipidemia is characterized by

hypertriglyceridemia, increased levels of very low density lipoproteins (VLDL), LDL-C and decreased levels of HDL-C[11].

Presence of thyroid dysfunction may affect diabetes control. Hyperthyroidism is typically associated with worsening of glycemic control and increase insulin requirements. In hypothyroidism, the synthesis and release of insulin is decreased. The rate of hepatic glucose output is decreased probably due to reduced gluconeogenesis[12,13].

Thyroid disorders are known to influence lipid metabolism. Overt or subclinical hypothyroidism is associated with hypercholesterolemia mainly due to elevation of LDL-C level, whereas HDL-C is usually normal or even elevated[14,15]. Abnormalities of lipid metabolism in hypothyroidism contribute to the development of CVD. Subclinical hyperthyroidism may increase the risk of cardiac arrhythmias and exacerbate angina. On the other hand, hyperthyroidism is accompanied by decrease in serum levels of total cholesterol, LDL-C and HDL-C[12]. HbA1c is normally used for assessment of diabetic control, and the American Diabetes Association recently recommended its use for diagnosing diabetes and pre-diabetes[16].

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. We aimed to evaluate association between thyroid dysfunction, lipid profile and glycosylated hemoglobin in type 2 diabetic patients.

MATERIALS AND METHODS

A cross sectional study was carried out on 100 type 2 diabetic patients. All the patients were confirmed diabetics who previously had fasting blood glucose levels >126 mg/dl on more than two occasions based on the American diabetes association(ADA) 2010 criteria for diagnosis of DM[17] and who were receiving treatment such as insulin, oral hypoglycemic drugs or physical exercise therapy for diabetes mellitus. General health characteristics such as age, sex, smoking status, menopausal status, alcohol consumption, and dietary habits (particularly as related to preference) were investigated by a self-administered questionnaire. The study excluded the patients having history of type 1 diabetes mellitus, those with known history of thyroid dysfunction and patients with liver disease, renal disease, hypertension and pregnancy. All subjects were informed about the objectives of the study and what roles they were expected to play. This study was approved by institutional ethical committee.

Biochemical investigations:

Collection of blood sample: Under all aseptic precautions, using a sterile disposable syringe about 5 ml of venous blood was drawn from subjects after overnight fasting. 3 ml of blood was taken into plain vacutainer and was subjected for centrifugation, serum was separated which was used for estimation of FSG, thyroid profile and lipid profile. 2 ml blood was taken into EDTA containing vacutainer and was used for estimation of HbA1c.

Methods of estimation: FSG was measured by Glucose oxidase (GOD-POD) method [18]. Serum T_3, T_4 and TSH were estimated by Chemiluminescence Immunoassay Method (CLIA) in CLIA analyzer[19]. Serum TC, TAG and HDL-C were measured by enzymatic method using phenol-aminoantipyrine. Serum LDL cholesterol was determined using Friedwald's formula[20]. HbA1c is by Cation-Exchange resin method and the kit was purchased from Euro diagnostics Bangalore[21]. FSG and Lipid profile were estimated in Auto analyzer ERBA MANNHEIM EM 200 and HbA1c in Semiautoanalyzer ERBA Chemtouch.

Classification of the values into high, low, or normal thyroid hormone level was based on the following criteria. Subjects classified as having high levels of thyroid hormones had T_3 values >2ng/ml, T_4 value > 12µg/dl or TSH< 0.2 µIU/ml or both. Those classified as having hypothyroidism had T_3 values < 0.5 ng/ml, T_4 values < 4.8 µg/dl or TSH values >5.4 µIU/ml or both. Subject grouped as euthyroid had T_3, T_4 and TSH values within the range of 0.5 – 2.0 ng/ml, 4.8 – 11.6 µg/dl and 0.28 – 5.45 µIU/ml respectively.

For serum lipid reference level, National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) guideline was referred. According to NCEP-ATPIII guideline, hypercholesterolemia is defined as TC>200 mg/dl, high LDL-C when value >100 mg/dl, hypertriglyceridemia as TAG >150 mg/dl and low HDL-C when value <40 mg/dl. Dyslipidemia was defined by presence of one or more than one abnormal serum lipid concentration[22].

STATISTICAL ANALYSIS

Results are expressed as Mean ± SD, and range values for continuous data, number and percentage for discrete data. Prevalence of thyroid dysfunction was expressed as percentage with 95% confidence interval (CI). One way ANOVA was used for multiple group comparison, followed by Post hoc-Turkey's test for group wise comparison. Unpaired t-test was used for two group comparison. For all the tests P value of < 0.05 was considered for statistical significance. SPSS version 16 was used for data analysis.

RESULTS

Among the 100 type 2 diabetic patients studied, 47 were males and 53 were females with mean age of 55.5 ± 6.2 years. Graph 1 shows that among the 100 type 2 diabetic patients studied, 32% of the patients have abnormal thyroid hormone levels and 68% have normal thyroid hormone levels. Among the 32% of diabetic patients with abnormal thyroid hormone levels, 22% of them have hypothyroidism (8% clinical hypothyroidism, 14% subclinical hypothyroidism) and 10% of patients have hyperthyroidism (4% clinical hyperthyroidism, 6% subclinical hyperthyroidism). This is in accordance with studies[1,5,8-10].

After the thyroid function test the patients are categorized into two groups based on thyroid hormone levels.

Group I: Diabetic patients with normal thyroid hormone levels (Euthyroid diabetics).

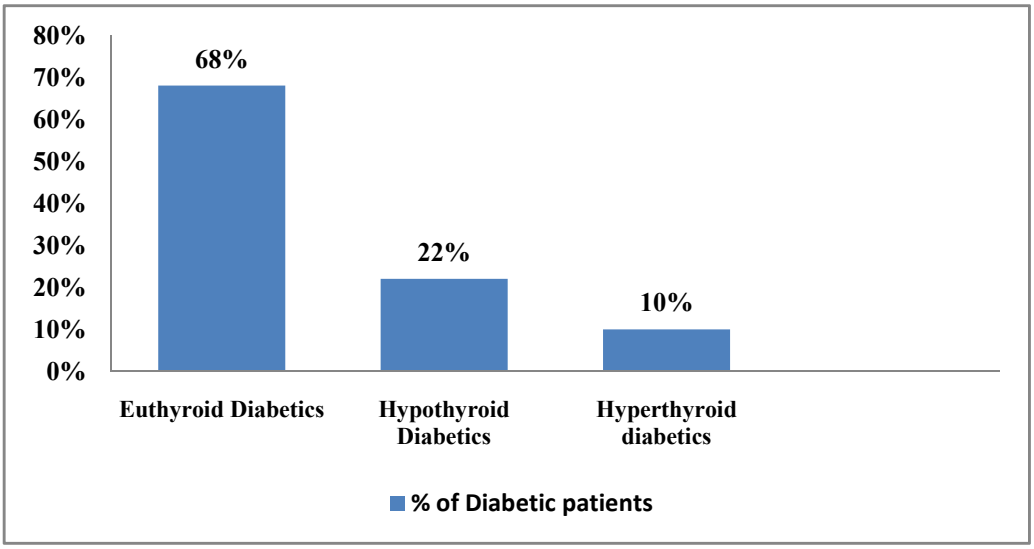
Group II: Diabetic patients with thyroid dysfunction (including both Hyperthyroidism and Hypothyroidism).

Table 1. Shows that the levels FSG, HbA1c, TC, TAG and LDL-C were increased in diabetic patients with thyroid dysfunction when compared to diabetic patients with euthyroidism and is of statistical significant (p<

0.001),whereas serum HDL-C level is decreased and is of statistical significant (p<0.001).

S- Significant NS- Non significant

The levels of FSG, HbA1c, TG, TAG, LDL-C and HDL-C did not differ significantly between diabetic patients with hypothyroidism and hyperthyroidism (p> 0.05).



Graph 1: Prevalence of thyroid dysfunction in type 2 diabetic patients

Table 1: Shows levels of FSG, HbA1c and lipid profile in diabetic patients with euthyroidism and diabetic patients with thyroid dysfunction

Parameters	Group I (Diabetics with Euthyroidism n=68)	Group II (Diabetics with thyroid dysfunction n=32)	Mean difference	t value	p value
FSG (mg/dl)	149.5±12.3 124-177	195.8±21.6 160-250	46.3	12.49	< 0.001
HbA1c (%)	8.1±0.6 6.9-10.2	11.2±1.1 9.6-13.6	3.1	16.5	< 0.001
TC (mg/dl)	217±22.5 165.7-265.6	273.6±38.7 185.6-375.1	56.7	8.5	< 0.001
TAG (mg/dl)	185.4±38.7 112.1-189.6	230.5±57.4 96.3-406.4	45.1	4.42	< 0.001
LDL-C (mg/dl)	143.1±30.6 84.4-262.6	195.8±37.6 126.9-280.9	52.7	7.47	< 0.001
HDL-C (mg/dl)	38.2±7.2 27.1-59.8	32.5±6.1 20.2- 43.5	5.7	4.27	< 0.001

Table 2: Shows levels of FSG, HbA1c and lipid profile in type 2 diabetic patients with hypothyroidism and hyperthyroidism

Parameters	Diabetics with Hypothyroidism (n=27)	Diabetics with Hyper thyroidism (n=15)	Mean difference	t value	p value
FSG (mg/dl)	193±23.2 160-250	200.9±18.1 170-241	7.9	1.22	0.23 NS
HbA1c (%)	11.1±1.1 9.6-13.6	11.2±1.1 9.8-13	0.1	0.28	0.78 NS
TC (mg/dl)	280.3±38.2 216.4-375.1	261.5±38.0 185.6±327.2	18.8	1.53	0.14 NS
TAG (mg/dl)	230.8±48.9 154.4-314.9	229.9±72.3 96.3-406.4	0.9	0.04	0.97 NS
LDL-C (mg/dl)	204.7±36.9 137.5-280.9	179.6±34.3 126.9-244.8	25.1	2.21	0.05 NS
HDL-C (mg/dl)	32.4±6.1 20.2-43.5	32.7±6.3 21.3- 40.8	0.3	0.17	0.86 NS

DISCUSSION

The present study has shown a very high prevalence of thyroid dysfunction among type 2 diabetic patients, hypothyroidism being more common than hyperthyroidism. Our results are in accordance with Pasupathi P et al[1], Singh G et al[5], Mazin Z et al[8], Swamy RM et al[9], C.E.J Udiong et al [10] and sheikh AW et al[23].

Several studies have been conducted to find out the mechanism of thyroid dysfunction in diabetic patients. 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 tissues. The presence of both raised and low levels of thyroid hormones levels in diabetics may also be due to modified TRH synthesis and release and may depend on the glycemic status of the diabetics studied. Glycemic status is influenced by insulin, which is known to modulate TRH and TSH levels. Stress, which is associated with diabetes, may also cause changes in the hypothalamus-anterior pituitary axis in diabetics. Marked hyperglycemia and hyperinsulinemia are known to suppress hepatic enzyme $T_{4\text{-}5}$ deiodinase, leading to decrease conversion of T_4 to T_3. Insulin has been associated with anabolic activity, enhance TSH turn over a protein hormone. Some of the oral hypoglycemic agents commonly used by the diabetic patients such as phenylthioureas are known to suppress the level of FT_4 and T_4, while causing raised levels of TSH[8,10].

Table 1. Shows that the levels of fasting serum glucose and HbA1c in type 2 diabetic patients with thyroid dysfunction were increased as compared to diabetic patients with euthyroidism and is of statistical significant ($p < 0.001$). Thyrotoxicosis is diabeticogenic factor and long term thyrotoxicosis has been shown to cause B-cell dysfunction. In hyperthyroidism there is elevation in the rate of glucose absorption, production (and utilization) and glycogen degradation leading to decreased glycogen level, but insulin resistance, degradation and requirements are increased and there is increased secretion with exaggerated effects of glucagon 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.

In hypothyroidism there is reduction in the rate of glucose absorption, gluconeogenesis and glucose production (and utilization) and glycogen synthesis 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[8].

The mean levels of TC, TAG and LDL-C were increased in diabetic patients with thyroid dysfunction as compared to diabetic patients with euthyroidism and is of statistical significant ($p< 0.001$), whereas HDL-C level is decreased and is of statistical significant ($p < 0.001$). These results are in consistent with previous studies[13,24]. But our study failed to show any significant difference between the levels of FSG, HbA1c and lipid profile in diabetic patients with Hypothyroidism and hyperthyroidism. Further studies are required to find out effect of thyroid dysfunction in type 2 diabetic patients.

Several factors are likely to be responsible for diabetic dyslipidemia: insulin effects on liver apoprotein production, regulation of lipoprotein lipase (LpL), actions of cholesteryl ester transfer protein (CETP), and peripheral actions of insulin on adipose and muscle[25].

Thyroid hormones influence all aspects of lipid metabolism including synthesis, mobilization, and degradation. Thyroid hormones regulate the activity of some key enzymes of lipid metabolism such as 3-hydroxy-3-methylglutaryl coenzyme A reductase, cholesteryl ester transfer protein, lipoprotein lipase, and hepatic lipase and also the expression of LDL receptors.

Hence diabetes mellitus when associated with thyroid dysfunction leads to further deterioration in glycemic control and lipid levels causing poor response to treatment.

Several studies have linked hyperlipidemia with cardiovascular morbidity. So thyroid function may have a role in the treatment of hyperlipidemia and can prevent associated cardiovascular morbidity[13].

Yang GR et al demonstrated that diabetic patients with subclinical hypothyroidism are found to have increased risk for developing retinopathy[26]. So it is important to evaluate diabetic population regarding thyroid disorders whether clinical or subclinical, as one condition can worsen the other if left untreated by causing worsening control of diabetes mellitus, worsening dyslipidemias and causing diverse complications.

CONCLUSION

Our findings indicate that thyroid dysfunction can produce significant metabolic disturbances among patients with type 2 DM. Screening of thyroid dysfunction should be done in all type 2 diabetic patients so that timely intervention can be done and patient's health can be improved.

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