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EVALUATION OF THYROID FUNCTION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS.

Biochemistry

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ABSTRACT

Introduction: Diabetes mellitus and thyroid disorders are the most common endocrinal disorders seen in clinical practice. The presence of undetected thyroid dysfunction may affect glycemic control in diabetics.
The aim of the present study was to evaluate the thyroid functions tests in patients with type 2 diabetes mellitus (T2DM).
Materials &methods: In this retrospective study we included diabetic patients who performed thyroid function tests i.e. free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) and the thyroid dysfunction was stratified as hypothyroidism, subclinical hypothyroidism, hyperthyroidism, subclinical hyperthyroidism with reference to hormonal levels.
Results: Prevalence of thyroid dysfunction in T2DM patients increases with age. Prevalence is higher if the patient has uncontrolled T2DM. Hypothyroidism is present 3.8% of diabetics and subclinical hypothyroidism is present in18.8% of diabetics. Hyperthyroidism is present in 61 % of diabetics and subclinical hyperthyroidism is present in 13.4 % of diabetics .Of the diabetic groups 3% were euthyroid.
Conclusions: Greater the duration of uncontrolled T2DM in a patient, higher is the chance of thyroid dysfunction. Females and advanced aged patients are more vulnerable to thyroid dysfunction. These data reinforce that diabetes patients with thyroid comorbidity need more endocrine attention.HbA1c can be used as a test to decide if screening for thyroid dysfunction is needed in T2DM patients or not.

KEYWORDS

Diabetes , Hypothyroidism, Hyperthyroidism, FT3, FT4,TSH

Introduction

The WHO estimate of diabetes prevalence for all age groups world wide was 2.8% in 2000 and 4.4% in 2030. Thyroid disease is common in the general population, and the prevalence increases with age 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.

Thyroid diseases have been described to be more common in diabetes than expected. Diabetic patients have a higher prevalence of thyroid disorders compared with the normal population. Because patients with one organ-specific autoimmune disease are at risk of developing other autoimmune disorders, and thyroid disorders are more common in females , type 2 diabetic patients.[1,2]

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 [3]. Type 2 diabetes mellitus (T2DM) appears to influence thyroid function in two sites; firstly at the level of hypothalamic control of TSH release and secondly at the conversion of thyroxine (T4) to triiodothyronine (T3) in the peripheral tissue. Marked hyperglycemia causes reversible reduction of the activity and hepatic concentration of T4-5-deiodinase, low serum concentration of T3, elevated levels of reverse T3 and low, normal, or high level of T4 [4]. 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.

The presence of thyroid dysfunction may affect diabetes control. Hyperthyroidism is typically associated with worsening glycemic control and increased insulin requirements. There is underlying increased hepatic gluconeogenesis, rapid gastrointestinal glucose absorption, and probably increased insulin resistance. Indeed, thyrotoxicosis may unmask latent diabetes [5].

Thus, the study was designed with an objective to find out the relation between T2DM and thyroid dysfunction which may behold answers to various facts.

Materials & Methods

This was a hospital based study conducted in the Department of Biochemistry, Sree Narayana Institute of medical sciences, Ernakulam after getting ethical clearance from the hospital ethical committee. This retrospective study included diabetic patients who performed thyroid function tests i.e. free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid stimulation hormone (TSH) during the time period Januvary 2013 to June 2015 .Patients with incomplete thyroid function test were ex-cluded from the study. The age and sex of the subjects were also noted.

In present retrospective study, a total of 385 diabetic patients were enrolled from January 2013 to June 2015. Among these patients 261 were female and 124 were male. 2.0 ml of venous blood was collected from the subjects in plain vial was allowed to clot and centrifuged at 3000 rpm for 15 minutes.

Thyroid function test panel (FT3, FT4 and TSH) were assayed by the ELFA (Enzyme linked fluorescent assay) method using Vidas kit. FT3 and FT4 were assayed by competitive immunoassay method with a final fluorescent detection and TSH was assayed by sandwich immunoassay method with a final fluorescent detection . All three parameters were estimated by following the same standard protocol provided by the manufacturer (VIDAS).

Estimation of blood glucose was done by a method based on GOD/POD principle. Glycated haemoglobin (HbA1c) estimation was done by Mispa i2 reagent (Nephelometry ,Agappe)

The reference interval for FT3, FT4 and TSH were 2.6 – 5.4 pg/ml , 6.9 -12.6 pg/ml and 0.25—5.0 IU/ml respectively. Thyroid function is considered normal (Euthyroidism) when subjects were presented with normal FT3, FT4 and TSH. Abnormal thyroid function was further categorized as hyperthyroidism (Increased FT3, FT4 and decreased TSH), subclinical hyperthyroidism (increased FT3, FT4 and normal TSH), hypothyroidism (decreased FT3, FT4 and increased TSH), and subclinical hypothyroidism (decreased FT3, FT4 and normal TSH).

Statistical analysis

Data was analyzed by Software Package for Social Sciences version 21 (SPSS 21). Data were represented as percentage, frequency, mean and standard error, students unpaired t test, Pearsons correlation. Data were

considered significant at p<0.05

Results

In present retrospective study, a total of 385 subjects were enrolled from year January 2013 to June 2014. Among these subjects 261 were female and 124 were male. The subjects were classified according to thyroid status as hypo-thyroidism, hyperthyroidism,subclinical hypothyroidism, subclinical hyperthyroidism and euthyroidism taking reference of thyroid function test. Total hypothyroidism includes hypothyroidism plus subclinical hypothyroidism and total hyperthyroidism represents hyperthy-roidism and subclinical hyperthyroidism.

Of 195 T2DM patients, patients with HbA1c levels > 7 or FBS >126 mg/dl and PPBS >150mg/dl were considered as uncontrolled T2DM patients and studied in the case group whereas 190 patients of T2DM with HBA1C levels < 7 or FBS <126 mg/dl and PPBS <150 mg/dl were considered as controlled T2DM patients and studied in the control group.

Table 1: Sex and age distribution of diabetic subjects.

Sex	No	Mean age in years
Male	124	48.15±5.13
Female	261	46.05±4.99

Table-2: Comparison of Levels of FBS, PPBS, HbA1c in controlled & uncontrolled diabetic patients :

Parameters	Uncontrolled diabetes (n=195) Mean ± SD	Controlled diabetes (n=190) Mean ± SD	Student's Unpaired t test	p value
FBS	189.09±93.87	99.07± 34.72	14.381	<0.001
PPBS	240.61±93.11	133.29± 42.13	17.806	<0.001
HbA1c	8.8±1.31	5.66±0.79	19.679	<0.0001

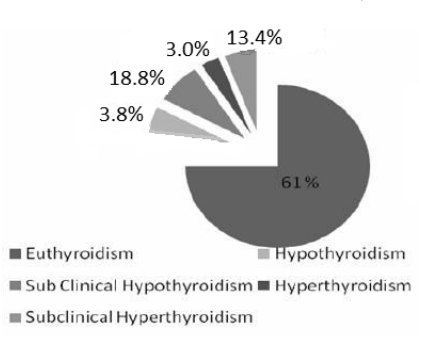
Table-3: Correlation between FBS, PPBS, HbA1C Levels and Thyroid Function Parameters in uncontrolled and controlled diabetes:

	Pearson's correlation coefficient value (r)					
	Uncontrolled diabetes			Controlled diabetes		
	FT3	FT4	TSH	FT3	Ft4	TSH
FBS	0.0212	- 0.0392	0.0817	-0.0868	- 0.0262	0.0693
p value	0.723	0.531	0.612	0.412	0.713	0.537
PPBS	0.086	0.023	-0.017	- 0.231	-0.143	0.0100
p value	0.442	0.750	0.785	0.0532	0.394	0.827
HbA1c	- 0.318	- 0.243	0.321	- 0.0692	- 0.0465	0.169
p value	0.002	0.026	0.003	0.523	0.721	0.132

Table 4: Comparison of Thyroid Functions Parameters in uncontrolled & uncontrolled diabetes.

Thyroid Functions Parameters	Uncontrolled diabetes Mean ± SD	Controlled diabetes Mean ± SD	p value
T3	5.5 ±2.2	3.8± 2.32	0.03
T4	12.51±3.37	9.26± 2.62	0.0002
TSH	1.68±6.84	2.10 ±2.31	<0.0001

Fig 1. The distribution of thyroid disorder in type 2 diabetes mellitus.



diabetic population. Our observation is in agreement with reports of Suzuki et al [6], Celani et al [7] and Udiang et al [8] who found altered thyroid hormone level of different magnitude in diabetic patients.

Compared the mean FBS, PPBS and HbA1c levels in the cases and controls (Table-1). Students unpaired t test was used. No significant difference was seen in the levels of FBS and PPBS but extremely significant difference between the mean HbA1c levels was seen.

To know if there existed any correlation between levels of FBS, PPBS, HbA1c levels and thyroid function parameters in cases and controls (Table-2). Karl Pearson's correlation coefficient was used. p values were > 0.05 for FBS and PPBS. Hence, no significant correlation was seen.

Discussion

Thyroid diseases and diabetes mellitus are the two most common endocrine disorders. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported [9, 10]. On one hand, thyroid hormones contribute to the regulation of carbohydrate metabolism and pancreatic function, and on the other hand, diabetes affects thyroid function tests to variable extents.

Thyroid hormones affect glucose metabolism via several mechanisms. Hyperthyroidism has long been recognized to promote hyperglycemia [11]. During hyperthyroidism, the half-life of insulin is reduced most likely secondary to an increased rate of degradation and an enhanced release of biologically inactive insulin precursors [12,13] .Untreated hyperthyroidism was associated with a reduced C-peptide to proinsulin ratio suggesting an underlying defect in pro-insulin processing [14]. Another mechanism explaining the relationship between hyperthyroidism and hyperglycemia is the increased absorption of glucose in gut mediated by the excess thyroid hormones [15,16].

Endogenous production of glucose is also enhanced in hyperthyroidism via several mechanisms. Thyroid hormones produce an increase in the hepatocyte plasma membrane concentrations of glucose transporter (GLUT2) which is the main glucose transporter in the liver and consequently the increased levels of GLUT2 contribute to the increased hepatic glucose output and abnormal glucose metabolism [17,18]. Additionally increased lipolysis is observed in hyperthyroidism resulting in an increase in free fatty acids (FFA) that stimulates hepatic gluconeogenesis. The increased release of FFA could partially be explained by an enhanced catecholamine-stimulated lipolysis induced by the excess thyroid hormones [19]. Moreover, the non-oxidative glucose disposal in hyperthyroidism is enhanced resulting in an overproduction of lactate that enters the Cori cycle and promotes further hepatic gluconeogenesis. The increase in growth hormone, glucagon and catecholamine levels associated with hyperthyroidism further contributes to the impaired glucose tolerance [20-22].

It is well known that diabetic patients with hyperthyroidism experience worsening of their glycemic control and thyrotoxicosis has been shown to precipitate diabetic ketoacidosis [23,24]. Chronic hyperglycemia from any route of cause leads to dyslipidemia ,elevated thyroid stimulating hormone, cardiovascular diseases, renal diseases, neurological problems and recurrent infections.

The present study reveals different grades of thyroid dysfunction among diabetes. Hypothyroidism is present 3.8% of diabetics and subclinical hypothyroidism is present in18.8% of diabetics. Hyperthyroidism is present in 61 % of diabetics and subclinical hyperthyroidism is present in 13.4 % of diabetics .Of the diabetic groups 3% were euthyroid. This goes in accordance with the reports of Suzuki et al[6] and Smithson et al[25] who found altered thyroid hormone level of different magnitude (both low and high) in diabetic patient. The abnormal thyroid hormone level may be the because of various medications the diabetics was receiving. For example, it is known that insulin an anabolic hormone enhances the level of FT4 while it suppresses the level of T3 by inhibiting hepatic conversion of T4 to T3 [26]. On the other hand some of the oral hypoglycemic agents such as the phenylthioureas are known to suppress the level of FT4 and T4, while causing raised levels of TSH [27, 28]. 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) synthesis and release may depend on the glycaemic status of the diabetics studied[29]. Glycaemic status is influenced by insulin, which is known to modulate TRH and TSH levels [30].

The thyroid hormones, tri-iodothyronine and tetra iodothyronine are insulin antagonists that potentiate the action of insulin indirectly by TRH synthesis which decreases in diabetes mellitus . These facts could be responsible for the occurrences of low thyroid hormone levels in some diabetics.

The diagnosis of thyroid dysfunction in diabetic patients based solely on clinical manifestations can be difficult. Poor glycemic control can produce features similar to hyperthyroidism, such as weight loss despite increased appetite and fatigue. On the other hand, severe diabetic nephropathy can be mistaken for hypothyroidism because patients with this condition may have edema, fatigue, pallor, and weight gain.

To further complicate the diagnostic process, poorly controlled diabetes, with or without its complications, may produce changes in thyroid function tests that occur in non-thyroidal illnesses. Typical changes include a low serum T3 due to impaired extrathyroidal T4 to T3 conversion, a low serum T4 due to decreased protein binding, and an inappropriately low serum TSH concentration.

However, the underlying thyroid dysfunction can produce clinically important physiological effects. Subclinical hypothyroidism can elevate serum LDL cholesterol and worsen pre-existing dyslipidemia, further increasing the risk of atherosclerosis. Subclinical hyperthyroidism may increase the risk of cardiac arrhythmias and exacerbate angina. Since diabetic patients are at high risk for cardiovascular diseases, the diagnosis and treatment of subclinical thyroid diseases is important.

Therefore, it seems prudent to consider thyroid function in newly diagnosed as well as chronic diabetic patients. Thyroid dysfunction is common in diabetic patients and can produce significant metabolic disturbances. Therefore, regular screening for thyroid abnormalities in all diabetic patients will allow early treatment of subclinical thyroid dysfunction. This raises the issue whether routine screening for thyroid disease in all patients newly diagnosed with diabetes mellitus will be cost effective.

Conclusion

This study show high incidence of abnormal thyroid hormone level among type 2 diabetic subjects. Thyroid dysfunction is common in diabetic patients and can produce significant metabolic disturbances. Therefore, regular screening for thyroid abnormalities in all diabetic patients will allow early treatment of subclinical thyroid dysfunction. Females and advanced aged patients are more vulnerable to thyroid dysfunction.. These data reinforce that diabetes patients with thyroid comorbidity need more endocrine attention. HbA1c can be used as a test to decide if screening for thyroid dysfunction is needed in T2DM patients or not Due to the retrospective design, the limited number of patients and the high percentage of missing data in some patient groups our results need to be interpreted with caution. Further studies are needed to confirm our findings and elucidate mechanisms of interaction of thyroid disease in type 2 diabetes patients.

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