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Thyroid Dysfunction In Patients With Type 2 Diabetes Mellitus

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Abstract

Background:
Both forms of thyroid dysfunction (Hyper or hypothyroidism) , may be associated with type 2 diabetes Mellitus and may affect the control of sugar in diabetic patients.

Aim of the study:
In the present study we investigated the prevalence of thyroid dysfunction and autoimmunity in patients with Type 2 diabetes Mellitus.

Patient and methods:
Seventy five type 2 diabetic patients and fifty control patients were enrolled in this study. They were recruited from patients who visited the counsultation room of internal medicine at AL-Kadhymia teaching hospital from March 2005 to October 2005 and agreed to have thyroid function test (T3, T4, TSH) and autoantibodies (thyroid peroxidase and thyroglobulin antibodies) to be done for them.

The patients results were compared with the results of the controls. Any acute medical illness, drugs that affect thyroid function test or thyroglobulin autoantibodies were excluded for both the patients and the controls. Also the patients or the controls that were pregnant or in puberty or postpartum periods were excluded

Results :
In this study we found that, the number of diabetic patients who were already known to have thyroid dysfunction was 5 (6.6 %) and the number of those with newly discovered thyroid dysfunction as a result of screening was 5 (6.6 %).

Thus the overall prevalence of thyroid disease in patients with type 2 DM was (13.3 %). The most common pattern of thyroid dysfunction was clinical hypothyroidism (6.6 %).

In the control group the prevalence was 6 % (N=3). The most common pattern was subclinical hypothyroidism (4 %).

There was insignificant difference in the prevalence of thyroid dysfunction between the diabetics and the control subjects and P value = 0.299, 0.265, 0.929 for T3, T4, TSH respectively.

Positive Thyroid peroxidase antibody was found in 6 diabetic patients (8 %) versus 4 in the control group (8 %) P=0.655. Positivity for both Thyroid peroxidase antibody and Thyroglobulin antibody was found in 2 diabetics (2.6 %) versus 2 in the control subjects (4 %) and the P- value= 0.171. Again there was insignificant difference between the diabetic patients and the control subjects.

Conclusion:
No significant difference in the prevalence of thyroid dysfunction and autoantibodies between type 2 diabetic patients and the control group.

Keywords: thyroid dysfunction, type 2 diabetes Mellitus, thyroid function test, Thyroglobulin antibody.

Introduction

Thyroxine (T4) is the major secretary product of the thyroid, with a daily production rate of 80-100 microgram. T4 is produced only by the thyroid gland. In contrast, only 20% of the daily production of tri-iodothyronine (T3) is derived from thyroid secretion and 80% from peripheral T4 conversion. The daily production rate of T3 is 30- 40 microgram. Normal thyroid hormone formation requires normal TSH levels and an adequate but not excessive supply of iodine. Optimal iodine intake is 150 – 300 microgram / day. In some mountainous areas of the world daily iodine supplies can be as low as 20 -30 microgram. For adults the recommended daily iodine dose is 150 microgram, which should increase to 200 microgram /d for pregnant woman. Iodine is reduced to iodide in the GIT and readily absorbed. Iodide is removed from the blood stream by uptake and concentration in the thyroid gland and excretion in the urine. The uptake of iodide into the thyroid cell is mediated by the sodium/iodide symporter (NIS). Under normal conditions, the kidney clears iodide from plasma at about 30 mL/min, whereas thyroid clearance is 8mL/min, so that only 25% of intake enters the thyroid under normal conditions. Excess iodine intake lowers the percentage of uptake; reduced intake raises it. Thyroid uptake of iodide varies from 5-30%. The ability of the thyroid to actively accumulate iodine through an iodide transporter localized in the cell membrane leads to a 20 to 40:1 concentration gradient of cell to plasma. The iodide in the thyroid cells is rapidly oxidized and enzymatically incorporated via thyroid peroxidase into tyrosine molecules of thyroglobulin by a process called organification. Thyroid peroxidase requires activation by H_2O_2. Antithyroid medications such as propylthiouracil (PTU) and methimazole inhibit thyroid peroxidase, thereby decreasing thyroid hormone formation. Thyroid hormone formation occurs on thyroglobulin, a 660-kD glycoprotein, with 25% of its tyrosine residues accessible to iodination. The monoiodinated tyrosine and the diiodinated tyrosine are coupled by the thyroid peroxidase enzyme to form T4 by linking two DIT or , for T3 formation , linking one monoiodinated tyrosine and one diiodinated tyrosine molecule(1).

Measurements Of Thyroid Hormone Values:

Total serum T4 and T3 measure the total amount of hormone bound to thyroid - binding proteins by radioimmunoassay. Total T4 and total T3 levels are elevated in hyperthyroidism and low in hypothyroidism. Increase in TBG increases the total T4 and T3 measured in the absence of hyperthyroidism. Similarly, total T4 and T3 are low in conditions associated with low TBG. Thus, further tests to assess the free hormone level that reflects biologic activity must be done. Free T4 level can be estimated by calculating the free T4 index (2).

The FTI is an indirect method of assessing free T4. It is derived by multiplying the total T4 by the T3 resin uptake, which is inversely proportional to the available T4 binding sites on TBG. Free T4 can be measured directly by dialysis or ultrafiltration. This is more accurate and is preferred to the FTI. Reverse T3 (normal range, 20-40 nanogram/dL) should be determined in special situations. Its level is elevated in patients with various systemic illnesses, leading to nonthyroidal illness syndrome. Because of decreased T4, free T4, and T3 levels in some of these patients, its determination can help to distinguish nonthyroid illness from hypothyroidism. In hypothyroidism reverse T3 is decreased (2).

Serum TSH is measured by a third – generation immunometric assay, which employs at least two different monoclonal antibodies against different regions of the TSH molecule, resulting in accurate discrimination between normal TSH levels and low TSH levels. Thus, the TSH assay can diagnose clinical and subclinical hyperthyroidism. In primary hypothyroidism, serum TSH is supranormal because of diminished feedback inhibition. In secondary or tertiary hypothyroidism, the TSH is usually low but may be normal (2).

Thyroid Dysfunction and Diabetes:

The presence of thyroid dysfunction may affect diabetes control. Hyperthyroidism is associated with worsening glycemic control and increased insulin requirements. There is increased hepatic

gluconeogenesis, rapid gastro-intestinal glucose absorption and probably increased insulin resistance. Thyrotoxicosis may unmask diabetes (5).

In hyperthyroid patients, the diagnosis of glucose intolerance needs to be considered cautiously, since hyperglycemia may improve with treatment of thyrotoxicosis. Underlying hyperthyroidism should be considered in diabetic patients with unexplained worsening hyperglycemia (5).

Although wide – ranging changes in carbohydrate metabolism are seen in hypothyroidism, clinical manifestations of these abnormalities is seldom conspicuous. However, the reduced rate of insulin degradation may lower exogenous insulin requirements. The presence of hypoglycemia is uncommon in isolated hypothyrpoidism and should raise the possibility of hypopituitarism (5). More importantly, hypothyroidism is accompanied by abnormalities in plasma lipid metabolisim. Even subclinical hypothyroidism can exacerbate the coexisting dyslipidemia commonly found in type 2 DM and further increase the risk of cardiovascular diseases(5)(8)(9).

Patients and Methods

The criteria for the diagnosis of type 2 diabetes mellitus as the American Diabetic Association criteria ; fasting blood glucose of ≥ 126 mg/dl , random blood glucose 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 or control subjects with diseases that may affect thyroid function test were excluded. All medications that affect TBG or interfere with thyroxine binding to TBG were excluded. Pregnancy, postpartum or pubertal periods were excluded.

We looked for signs and symptoms of thyroid disease , also we looked for features of pituitary disease so as to know that thyroid dysfunction was primary or secondary.

Seventy five T2DM patients and fifty control subjects were enrolled in this study. They were recruited from people who visited the consultation room of internal medicine at Al-Kadhymia teaching hospital from March 2005 to October 2005.

For the patients with T2DM , the number of males was 37 (49 %) and the number of females was 38 (51 %). The mean age was 49.8 ±7.8 year , and the age range was (37 - 65) years (table 2).

For the control group, the number of males was 25 (50 %) and the number of females was 25 (50%). The mean age was 48 ± 9.4 year , and the age range was (35 - 60)years. This group was neither diabetic nor had any endocrine or any illness that may affect TFT (table 2).

Venous blood samples were withdrawn and assayed for: total T4, total T3, TSH, thyroid peroxidase antibody, anti-thyroglobulin antibody. Serum was frozen at (-20) ^{o}C until analysis. Other antibodies like anti GAD, anti islet cell, anti beta cell antigen and anti insulin were not available.

Biochemical measurements:

Serum total T4 (normal range is 55- 170 nmol/l), serum total T3 (normal range is 1-3.3 nmol/l),and serum TSH (normal range is 0.3-3.8 micro IU / ml)were determined by RIA. Serum anti-TPO antibody (normal range is < 50 Iu / ml , 50 -70 is borderline , > 75 is elevated)and serum anti TG antibody (normal range is < 100 Iu / ml , 100 – 150 is borderline , > 150 is elevated) were determined by ELISA method.

The following guidelines for detection of thyroid dysfunction were considered (according to the standards of the hospital lab):

* Subclinical hypothyroidism: TSH>3.8 micro IU/ml with normal T3 and T4.
* Subclinical hyperthyroidism: TSH<0.3 micro IU/ml with normal T3 and T4.
* Overt hypothyroidism: low T3 and T4 with elevated TSH.
* Overt hyperthyroidism: high T3 and T4 with suppressed TSH.
* Antibodies were considered positive if they were above the range mentioned.

Statistical analysis:

The data was analyzed using SPSS version 10 and Excel. Results were expressed as mean , standard deviation and ranges. The prevalence of thyroid dysfunction and autoantibodies in T2DM patients and controls were compared using chi-square; the student T test compare the two groups with respect to continuous variables. P values < 0.05 was significant.

Results

Of the seventy five T2DM patients, 10 patients (13.3%) had thyroid dysfunction; five (6.6%) had previous thyroid disease and five were newly discovered. For those with previous disease four patients (5.3%) were hypothyroid on thyroxine replacement and one patient (1.3%) with hyperthyroidism on neomercazole. The four hypothyroid patients had primary hypothyroidism. Of these five patients four were females and one was a male (Table 1).

For those who are newly discovered cases: three (4%) had subclinical hypothyroidism, one (1.3%) had clinical hypothyroidism, one (1.3%) had subclinical hyperthyroidism. Three were females and two were males (Table 1).

The prevalence of the known and newly discovered thyroid dysfunction in females was (9.3%) while in males it was (4%) P= 0.196 .

In the age and sex matched control group the newly discovered cases were two subclinical hypothyroidism (both were females) and one subclinical hyperthyroidism (was a male) (Table 1). There was insignificant difference in the prevalence in thyroid dysfunction between T2DM patients and the control group P=0.299, 0.265, 0.929 for T3, T4, TSH respectively.

Table 1: shows patterns of thyroid dysfunction among diabetics and Control subjects.

Characteristics	Diabetics (N=75)	Control (N=50)	P value
Female	**38(51%)**	**25(50%)**	**0.86**
Male	**37(49%)**	**25(50%)**	**0.86**
Mean age ± SD (years)	**49.8 ± 7.8**	**48 ±9.4**	
Duration of T2DM± SD (years)	**6.2 ± 4.1**	**NA**	

Table 2: shows the number of diabetic patients and control subject, mean Age of each group and the duration of T2DM.

	Hypothyroidism	Subclinical hypothyroidism	Hyperthyroidism	Subclinical hyperthyroidism	Euthyroidism	total
Patient (n=75)						
Male (37)	**2(2.6%)**	**0**	**0**	**1(1.3%)**		**3(4%)**
Female (38)	**3(4%)**	**3(4%)**	**1(1.3%)**	**0**		**7(9.3%)**
P value	**0.734**	**0.734**				
Control Group						
Male (25)	**0**	**0**	**0**	**1(2%)**		**1(2%)**
Female (25)	**0**	**2(4%)**	**0**	**0**		**2(4%)**

Thyroid antibodies were available for the seventy five T2DM patients and for the fifty controls. In T2DM patients 6 (8%) patients had positive TPO antibody, and two patients (2.6%) had positive both TPO and TG antibodies. For those five patients with newly diagnosed thyroid dysfunction two patients (2.6%) had positive TPO and TG antibodies and both patients had subclinical hypothyroidism. One patient (1.3%) had positive TPO antibody only (Table 3).

For the remaining sixty five T2DM (neither had clinical nor subclinical thyroid dysfunction) no one was positive for both antibodies but positive TPO antibody only was present in three patients (4%) (Table 3).

Table 3: shows the prevalence of autoantibodies in T2DM patients and the Control subjects

Autoantibody	T2DM (N=75)		Control (N=50)		P value
	With dysfunction	Without dysfunction	With dysfunction	Without dysfunction	
Anti TPO positive	1(1.3%)	3(4%)	1(2%)	1(2%)	0.655
Anti TPO + TG positive	2(2.6%)	0	0	2(4%)	0.171

In the control group (N=50): four patients (8%) had positive thyroperoxidase antibody and only two subjects (4%) were positive for both thyroperoxidase and thyroglobulin antibody. For the three subjects with dysfunction only one had positive Thyroperoxidase antibody only (2%). For the rest of the control group (those without dysfunction) two subjects (4%) were positive for both antibodies TG and TPO, and only one subject (2%) was positive for TPO antibody only (Table 3).

Discussion

In the present study, we evaluated the prevalence of thyroid dysfunction in diabetic patients and whether it is significantly different from that in the control group. Also anti – thyroid antibodies were evaluated in the diabetic patients and control subjects and determined if there was a significant difference between the two groups. The prevalence of thyroid dysfunction in T2DM was 13.3% versus 6% in the control group. By comparing the mean value of T3, T4 and TSH between T2DM patients and that of the control subjects, the P values were 0.299, 0.265, 0.929 respectively. These values showed insignificant difference.

The prevalence of thyroperoxidase , thyroglobulin antibodies was compared between diabetic and control groups. The P values were 0.655, 0.879 respectively. This was insignificant. Positivity for both TPO and TG was 2.6% in T2DM versus 4% in the control group. P value =0.171. The prevalence of thyroid dysfunction in females was higher than that in males in T2DM patients. P value = 0.196. The most common pattern of thyroid dysfunction in T2DM patients was clinical hypothyroidism.

In a similar study carried out in Jordan, the prevalence of thyroid dysfunction in T2DM patients was 12.5% with P value = 0.0064 in comparison with the control group. Positive TPO antibody was found in 8.3% with P value = 0.412. Positivity for both antibodies was found in 2.5% of T2DM versus 6% of the control subjects with P value = 0.0155. The most common pattern of thyroid dysfunction in T2DM patients was subclinical hypothyroidism (4.1%). The prevalence of thyroid dysfunction in females with T2DM was 17.5% versus 6.5% in males with P value < 0.00006.

So this study showed significant difference in thyroid dysfunction in T2DM and significant difference in the prevalence of positivity for both antibodies (10).

A second study carried out in Iran, found a high and significant prevalence of thyroid dysfunction in patients with T2DM in particular those with uncontrolled diabetes mellitus, P value < 0.01. The observed disorder in thyroid function and size included goiter (30%), subclinical hypothyroidism (13%) , hypothyroidism (4%) and hyperthyroidism (0.5%). Thyroid antibodies were not evaluated in this study (11).

In a third study carried out in Spain, thyroid dysfunction was significantly high in T2DM patients P value = 0.039. Thyroid dysfunction and autoimmune thyroiditis prevalences were higher in females (P = 0.02, P = 0.018 respectively). More over thyroid dysfunction was positively associated with autoimmune thyroiditis (P = 0.001) and age (P = 0.026)(12).

A fourth study carried out in UK found that the prevalence of thyroid dysfunction in the entire population of diabetic patients registered in the general practice was 10.8%(13).

A fifth study in UK(14) which divided diabetic patients into four groups: G1 were clinically hypothyroid , G2 had elevated TSH and normal or low FTI , G3 had low TSH and low or normal FTI , and G4 had normal FTI and normal or low TSH. The study found higher and significant preponderance (P<0.01) in G1 and G2 of women patients and patients over 60 years. Thyroid antibodies were more common (P<0.05) in G1 and G2. In G3 there were significantly more men and patients under 40 years of age (P<0.01). The prevalence of hypothyroidism was 4%. The high prevalence of abnormal TFT may result from high prevalence (26%) of thyroid antibodies. Thirty percent of diabetics had increased TSH (G2) but no evidence of clinical hypothyroidism.

From the above studies they conclude that diabetic patients showed a higher prevalence of thyroid dysfunction. In some studies the prevalence of thyroid antibodies were higher in diabetic patients and their presence may necessitate treatment of subclinical hypothyroidism. So all these studies recommended screening for thyroid dysfunction in diabetic patients.

Another study carried out in Australia which evaluated the prevalence and progression of subclinical hypothyroidism in women with T2DM found that the prevalence of subclinical hypothyroidism was 8.6% and it was associated with anti TPO status and age. In the subgroup of patients restudied after five years , none of those who had subclinical hypothyroidism at baseline had overt hypothyroidism regardless of anti TPO status. So this study concluded that in women with T2DM without known thyroid disease, subclinical hypothyroidism is a common but incidental finding and routine screening of thyroid function in T2DM is questionable(15).

The insignificant results obtained in my study may be explained by the smaller sample size included in the study in comparison with other studies.

Conclusion

No significant difference in the prevalence of thyroid dysfunction and autoantibodies between T2DM patients and the control group.

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