Diabetes Mellitus and Thyroid Disorders

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داء السكري والاضطرابات الدرقية

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الملخص

تمهيد: داء السكري وأمراض الغدة الدرقية هما الأكثر شيوعاً عند البالغين. الأنسولين وهرمونات الغدة الدرقية يؤثران على أعمال بعضهم البعض. إن داء السكري قد يؤثر على اختبارات وظيفة الغدة الدرقية وهناك العديد من الاضطرابات الدرقية قد تكون موجودة مع داء السكري.

الأهداف: لتحديد تأثير داء السكري على الحالة الدرقية ولدراسة تردد الاضطرابات الدرقية في المرضى المصابين بداء السكري والعلاقة بين الاضطرابات الدرقية والعلاج ضد السكري.

الطرق: هذه الدراسة شملت ٤١٥ مريض مصاب بداء السكري والذين راجعوا العيادة الخارجية لمرض السكري في مستشفى الديوانية التعليمي وتمت دراستهم خلال الفترة من الأول من كانون الثاني/ ٢٠٠٩ إلى الثلاثون من أيلول/ ٢٠٠٩. تم تقيم الحالة الدرقية لدى جميع المرضى.

النتائج: وجدت أشكال الدرقية الشاذة في ١٦.٨٦ % من المرضى ووجد العطل الدرقي في ٢٣.٦ % من المرضى (زيادة أو نقص في إفراز الغدة الدرقية السريري أو دون السريري ومتلازمة اعتدال الدرقية المريضة-SES- بنسبة ٤.٣ %، ٤.١ %، ٣.١ %، ٦.٨ % و ٥.٣ % على التوالي).

الاستنتاجات: بينت هذه الدراسة زيادة في الاضطرابات الدرقية وزيادة هامة في أشكال الدرقية الشاذة في المرضى المصابين بداء السكري (اناث في الغالب) والذين يتناولون العلاج الفموي ضد السكري(OAD). يجب عمل الفحص الروتيني للاستدلال على حالات الشذوذ الدرقية لدى المرضى المصابين بداء السكري.

Abstract:

Background: Diabetes mellitus (DM) and thyroid diseases are the most common endocrine disorders seen in adults. Insulin and thyroid hormones affect the actions of each other. DM may affect thyroid function test and there are many thyroid disorders that may present with DM.

Objectives: To determine the influence of DM on thyroid state and to study: the frequency of thyroid disorders in diabetic patients and the relation between thyroid disorders and antidiabetic treatment.

Methods: This study enrolled 415 diabetic patients who attend to the out patient clinic of DM at Al-Diwaniya Teaching Hospital, they were studied during the period from 1st of January 2009-30th of September 2009. All patients were assessed for thyroid state.

Results: Abnormal thyroid morphology (ATM) was found in 16.86% of patients and thyroid dysfunction was found in 23.6% of patients (clinical, subclinical hyper or hypothyroidism and sick euothyroid syndrome-SES-, were 4.3%, 4.1%, 3.1%, 6.8% and 5.3% respectively).
Conclusions: This study shows increase of thyroid disorders and increase of ATM in diabetic patients (mostly females) who were treated with oral antidiabetic (OAD). Routine screening for evidence of thyroid abnormalities in diabetic patients should be done.

Introduction

DM is a clinical syndrome characterised by hyperglycemia due to absolute deficiency of insulin (type 1 diabetes) or relative deficiency (type 2 diabetes and gestational diabetes) with different other specific types due to genetic defect of B-cell function or insulin, pancreatic diseases, drug-induced, viral infection, increase production of hormonal antagonist to insulin and specific syndromes. DM occurs world-wide and the incidence of both type 1 and type 2 are rising; 171 million people had diabetes in 2000, and this expected to double by 2030[(1)].

Many studies show that the prevalence of thyroid diseases is higher in diabetic patients than general population[(2)]. Understanding anatomical and physiological bases of both pancreas (islet of Langerhans) and thyroid gland allows the physician to understand specific assessment and rapid identification of thyroid disorders in diabetic patients. Thyroid hormones are insulin antagonists, both insulin and thyroid hormones involved in cellular metabolism and excess or deficit of any one can result in functional derangement of the other[(3)].

Thyroid disease is a pathological state adversely affect diabetic control and commonly found in most forms of DM which is associated with advanced age in type 2 diabetes and autoimmune disease in type 1 diabetes[(4)]. DM appears to influence thyroid function in two sites; firstly at the level of hypothalamic control of thyroid stimulating hormone (TSH) release and secondly at the conversion of tetraiodothyronine (T4) to triiodothyronine (T3) in the peripheral tissue[(4)]. Marked hyperglycemia causes reversible reduction of the activity and hepatic concentration of T4-5-deiodinase, low serum concentrations of T3, elevated levels of reverse T3 and low, normal, or high levels of T4[(4)].

T4 (total and free) and T3 concentrations may be inappropriately normal when hyperthyroidism present in patient with poorly diabetic control making some diagnostic difficulties which is supported by suppressed serum basal TSH or an absolutely flat response to thyrotropic releasing hormone (TRH)[(5)].

The presence of hyperthyroidism should be suspected in diabetic patients with or without thyroid enlargement in the presence of unexplained weight loss, supraventricular tachycardia, increased body temperature, heat intolerance, tremor, unexplained increase in insulin requirement, ketoacidosis and uncontrolled diabetic state despite strict antidiabetic treatment[(6)]. In addition to, poor glycemic control can produce similar features to hyperthyroidism such as weight loss despite increased appetite and fatigue. Severe diabetic nephropathy can be mistaken for hypothyroidism because patients may have oedema, fatigue, pallor and weight gain[(7)]. Sulfonylureas has an important goiterogenic effect on thyroid gland and this may affect the prevalence of goiter in diabetic patients[(8)].

In euthyroid diabetic patient, serum T3 levels and basal TSH levels with its response to TRH is influenced by glycemic status and poorly controlled diabetes may induce reversible “low T3 state”[(9)].

In hyperthyroidism glucose level is not always changed and the effect of thyroid hormones on carbohydrate metabolism may lead to disruptions of diabetic control and there is abnormal response in glucose tolerance test because glucose rises faster than in normal person[10] Graves' disease is the commonest cause of hyperthyroidism and may be associated with type 1 diabetes in autoimmune polyglandular syndrome(APS). The incidence of dysthyroid optic neuropathy in diabetic patients with Graves' disease is 10 folds more than that seen in controlled Graves' orbitopathy[11] and there is mild improvement in the vision after treatment of diabetic patients with Graves' disease. The prevalence of Graves' disease in patients with type 1 diabetes had been reported in 2.7% males and 2–19% females[12]. Many authors recommended the measurement of antithyroid peroxidase (anti-TPO) antibodies in evaluating patients with subclinical hypothyroidism because those patients with positive antibody have a higher risk for developing overt thyroid disease[13].

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 synthesis (and degradation) leading to decreased glycogen level[9] 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 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 (and degradation) 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[14].

Nearly one third of all newly detected type 1 (immune mediated) diabetic patients have co-existent thyroid autoimmune (TAI) disease and high prevalence of thyroid dysfunction predominantly hypothyroidism (clinical or subclinical). Type 1 diabetes may be seen in association with hypothyroidism in patient with Down's syndrome, congenital rubella and sometimes in cases of haemochromatosis[15]. APS 2 is more common in females and occurs in early to middle adulthood which is characterised by autosomal dominant inheritance and presence of autoimmune Addison's disease, autoimmune thyroid disease (Graves' disease and Hashimotos thyroiditis) and immune mediated diabetes[16]. SES refers to abnormal thyroid function test in patients with severe systemic illnesses not caused by primary thyroid or pituitary dysfunctions and the patients have suppressed or normal TSH levels making some difficulties to determine whether the patient has secondary hypothyroidism or SES and measurement of other pituitary hormones may be useful in differentiation between them. There is no role for levothyroxine treatment in SES and no need for treatment of subclinical thyroid dysfunction state[17].

Methods

This study enrolled 415 diabetic patients (irrespective to its type) whose age 53 ± 0.4 years, 255 females (61.45%) and 160 males (38.55%) who had been attend out patient clinic of DM at Al-Diwaniya Teaching Hospital were evaluated; (36 patients were excluded because they refused to participate in this study). All patients had been

followed and evaluated for thyroid diseases with consideration to the age, sex, type of treatment, results of thyroid palpation and ultrasound, results of thyroid function test (T3, T4, TSH), duration of thyroid disease, duration of DM and their relations were ascertained. Thyroid ultrasound was done for every patient irrespective to the presence of goiter or not. TSH levels were taken in consideration to evaluate subclinical thyroid dysfunction. The consents of the patients and the official requirement were taken.

Results

Females to males ratio about 1.6:1(females age were 50.6±0.6y and males age were 55.4±0.2). 345 patients (83.13%) of the sample were normal and the remnant patients with ATM (diffuse goiter, solitary nodule, multinodular thyroid goiter and history of thyroidectomy were 5.3%, 6.02%, 4.1% and 1.45% respectively) as shown in table 1 (p-value=0.03).

Euothyroid diabetic patients were 317 (76.4%) and remnant patients have thyroid dysfunction (hyperthyroidism, hypothyroidism, subclinical hyperthyroidism, subclinical hypothyroidism and SES were 4.3%, 4.1%, 3.1%, 6.8% and 5.3% respectively) as shown in table 2 (p-value=0.015).

ATM was found in 70 patients (16.86%), 52 females (12.53%) and 18 males (4.33%).Thyroid dysfunction was found in 98 patients (23.6%), 57 females (13.73%) and 41 males (9.87%) as shown in table 3.

Table 4 shown distribution of thyroid morphology according to type of treatment. Patients treated with diet control, OAD and insulin were 59, 274 and 82 respectively. Patients treated with OAD shown normal finding, diffuse goiter, solitary nodule, multinodular goiter and thyroidectomy were 88.7%, 4%, 3.3%, 2.9% and 1.1% respectively (p-value=٠.٠٠٨).

Table 5 shown distribution of thyroid function according to type of treatment. Euoyhyroid patients treated with diet control, OAD and insulin were 43, 216 and 58 respectively and the remnant patient have abnormal thyroid function (p-value=0.6).

Table 6 shown distribution of diabetic patients with ATM according to type of treatment: diet control, OAD and insulin were 17 (4.09%), 31 (7.47%) and 22 (5.3%) respectively. Patients with thyroid dysfunction treated with diet control, OAD and insulin were 16 (3.85%), 58 (13.97%) and 24 (5.78%) respectively.

Diabetic patients with ATM were 16 patients (3.85%) having thyroid disease before diagnosis of DM, 9 patients (2.17%) with simultaneous diagnosis of both and 45 patients (10.84%) having thyroid disease after diagnosis of DM as shown in table 7 (p-value=0.02).

Table 1. Distribution of thyroid morphology in diabetic patients

Thyroid morphology	Females		Males		Total		P-value
	No.	%	No.	%	No.	%	0.03*
Normal	203	79.6	142	88.75	345	83.13	
Diffuse goiter	18	7.06	4	2.5	22	5.3	
Solitary nodule	22	8.63	3	1.9	25	6.02	
Multinodular goiter	7	2.75	10	6.25	17	4.1	
Thyroidectomy	5	1.96	1	0.6	6	1.45	
Total no.	255	100	160	100	415	100	

*P-value less than 0.05 is considered significant.

Table 2. Distribution of thyroid function in diabetic patients

Thyroid function	Females		Males		Total		P-value
	No.	%	No.	%	No.	%	0.015*
Euothyroid	198	77.64	119	74.375	317	76.4	
Hyperthyroidism	8	3.14	10	6.25	18	4.3	
Hypothyroidism	15	5.88	2	1.25	17	4.1	
Subclinical hyperthyroidism	5	1.96	8	5	13	3.1	
Subclinical hypothyroidism	22	8.63	6	3.75	28	6.8	
SES	7	2.75	15	9.375	22	5.3	
Total no.	255	١٠٠	160	١٠٠	415	١٠٠	

Table 3. Distribution of diabetic patients with ATM and thyroid dysfunction according to gender

Diabetic patients	ATM		Thyroid dysfunction	
	No.	%	No.	%
Females	52	12.53	57	13.73
Males	18	4.33	41	9.87
Total no.	70	16.86	98	٢٣.6

Table 4. Distribution of thyroid morphology in diabetic patients according to type of treatment

Thyroid morphology	Diet		OAD		Insulin		P-value
	No.	%	No.	%	No.	%	٠.٠٠٨*
Normal	42	71.2	٢٤٣	88.7	60	73.2	
Diffuse goiter	٤	6.8	١١	4	٧	8.5	
Solitary nodule	٧	11.9	٩	3.3	٩	11	
Multinodular goiter	٤	6.8	٨	2.9	٥	6.1	
Thyroidectomy	٢	3.3	٣	1.1	١	1.2	
Total no.	٥٩	١٠٠	٢٧٤	١٠٠	٨٢	١٠٠	

Table 5. Distribution of thyroid function in diabetic patients according to type of treatment

Thyroid function	Diet		OAD		Insulin		P-value
	No.	%	No.	%	No.	%	0.6
Euothyroid	43	72.9	216	78.8	58	70.73	
Hyperthyroidism	3	5.1	13	4.7	2	2.44	
Hypothyroidism	2	3.4	11	4	4	4.88	
Subclinical Hyperthyroidism	1	1.7	7	2.6	5	6.1	
Subclinical Hypothyroidism	6	10.2	15	5.5	7	8.54	
SES	4	6.7	12	4.4	6	7.31	
Total no.	٥٩	١٠٠	٢٧٤	١٠٠	٨٢	١٠٠	

Table 6. Distribution of diabetic patients with ATM and thyroid dysfunction according to type of treatment

Type of treatment	ATM		Thyroid dysfunction	
	No.	%	No.	%
Diet	17	4.09	16	3.85
OAD	31	7.47	58	13.97
Insulin	22	5.3	24	5.78
Total no.	70	16.86	98	23.6

Table 7. Time relation between diagnosis of DM and thyroid disease in diabetic patients with ATM

Diabetic patients with ATM	Thyroid disease before DM	Simultaneous diagnosis of both	Thyroid disease after DM	P-value
Female	15 (3.61%)	4 (0.97%)	33 (7.95%)	0.02*
Male	1 (0.24%)	5 (1.2%)	12 (2.89%)	
Total no.	16 (3.85%)	9 (2.17%)	45 (10.84%)	

Discussion

The fact that DM reduce TRH and TSH levels otherwise OAD and insulin modulate their synthesis. Thyroid disorders are highly prevalent in the general population and usual thyroid function test may be influenced by common factors unrelated to thyroid disease (including: age, drugs, stress, psychological upset, pregnancy, obesity, DM and other diseases)[18]. The effects of DM on thyroid function appear more complex and impaired TSH response to TRH or lack of nocturnal TSH peak have been described in patients with uncontrolled DM[19].

Thyroid function test may change with no clinical dysfunction in euthyroid diabetic patients leading to subclinical hyper or hypothyroidism and SES with no need for treatment. The prevalence of thyroid diseases in general population were 6.6% and affect 10-15% of diabetic patients vs. non diabetic were 6% with predominance of hypothyroidism[20].

This study revealed that the frequency of hyperthyroidism and hypothyroidism in diabetic patients were 4.3% and 4.1% respectively, this result is in agreement with study done by Dimitriadis et al[21] who reported that the frequency of hyperthyroidism and hypothyroidism in diabetic patients was varied from 3.2 % to 4.6 % and 0.7 % to 4.0 % respectively.

Our study reported that ATM were found in 16.87% of diabetic patients (female were 12.53% and male were 4.34%) which is consistent with other studies done by Mouradian et al[22] had shown that the results of goiter from 3.4 % to 17 % and Canaris et al[23] reported goiter in 18.5% of diabetic patients.

Thyroid dysfunction were found in 23.6% of diabetic patients (females were 13.73% and males were 9.87%) with low incidence of hyperthyroidism in females (3.14%) in comparison to males (6.25%) but hypothyroid state was found higher in females (5.88%) than in males (1.25%). In studies done by Smithson MJ et al at primary care centers in England recorded variable levels of thyroid hormones in diabetic patients and the prevalence of thyroid dysfunction were 11% in patients with DM[24].

The results of this study also was supported by studies of Suzuki J et al[25] and Celani et al[26] who found altered thyroid hormones levels in diabetic patients. Sacks[27] reported that the incidence of hyperthyroidism were lower in females (8%) than males (11%) but the incidence of hypothyroidism were higher in females (16.8%) than males (9.9%) because TSH level were increased and decreased in diabetic females and males respectively.

This study showed significant difference of ATM in diabetic patients regarding types of treatment (mostly OAD) but with no significant difference in thyroid function. This indicated that the type of antidiabetic treatment have a good effect on thyroid morphology only, these results are not consistent with the report of Alexander et al studies[28] who reported increased both ATM and thyroid dysfunction in diabetic patients. Many investigators reported that treatment of DM with sulfonylurea may lead to increased incidence of goiter and hypothyroidism[8]. Failure to recognize presence of abnormal thyroid hormone levels in diabetics act as a primary cause of poor management in some treated patients. Therefore, there is need for routine assay of thyroid hormones in diabetic patients particularly those patients with comorbid conditions[29].

Conclusion

Inadequate treatment or untreated thyroid disease will adversely influence diabetic control. In addition to, the prevalence of thyroid disease is common in diabetic patients and can produce significant metabolic disturbances. Therefore, regular screening for thyroid function in all diabetic patients will allow early recognition of thyroid disorders. A sensitive serum TSH assay is the screening test of choice.

Recommendations

* Thyroid function test should be done to every diabetic patient with poorly controlled glycemic state.
* Screening TSH in women of childbearing age before pregnancy or during the first trimester when they had a history of gestational diabetes.
* Routine screening for TAI disease in all newly detected type 1 diabetes and investigate for anti-TPO antibodies at time of diagnosis with annual TSH screening when the test is positive.
* Annual TSH assessment in diabetic patients with subclinical thyroid dysfunction and SES.

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