Research Article

Thyroid functions abnormalities in Patients with Type 2 Diabetes Mellitus and its Relation to Diabetic Microvascular Complications

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Abstract
Background: Thyroid diseases and diabetes mellitus (DM) are the two most common endocrine disorders encountered in clinical practice. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported[(1)].
Aim of the study: the aim of this study is to detect thyroid function abnormalities in patients with type 2 diabetes mellitus and its relation to diabetic micro-vascular complications. **Subject and Methods**: all subjects were examined clinically to detect manifestation of any thyroid disorders including hypo and hyperthyroidism. We measured the level of thyroid hormones, lipid profile andalbumin creatinine ratio (A/C), fundus examination and neurological examination to detect diabetic microvascular complications in 80 patients with type 2 DM and 20 healthy volunteer as control group. The study detected thyroid function abnormalities and its relation to diabetic microvascular complications. **Results:** Out of 80 diabetic patients studied, 30 patients (37.5%) had abnormal thyroid functions, distributed as follow: 11 patients (13.75%) had subclinical hypothyroidism, 14 patients (17.5%) had overt hypothyroidism, 1 patient (1.25%) has subclinical hyperthyroidism (SCH) and 4 patients (5%) had overt hyperthyroidism. The thyroid abnormalities were predominant in females as 23 out of 30 patients with thyroid disorders were females(28.75%), Also the incidence of diabetic retinopathy was higher in diabetics with thyroid dysfunctions than diabetics without thyroid dysfunction(63.3%vs 46%)), The same for diabetic nephropathy (53.3% vs 48%).**Conclusion:** Diabetes has an important effect on development of thyroid function abnormalities and these abnormalities contribute to increased risk of micro vascular complications of diabetes.
Key words: DM, microvascular complications, thyroid disorders.

Introduction
Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice, Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported**.** Several reports documented a higher than normal prevalence of thyroid dysfunction in the diabetic population[(1)]. Thyroid function contributes to normal retinal vascular density. Further, hypothyroidism can play a permissive role in the development of retinal neo-vascularization**[(2)].** Furthermore SCH has been reported to be associated with endothelial dysfunction independent from other well-known atherosclerotic risk factors**[(3)].** It has been unequivocally apparent that testing for thyroid dysfunction in T2DM patients is necessary and should be carried out**[(4)].** The "American Thyroid Association" guidelines for T2DM patients require frequent testing for thyroid dysfunction. They recommend testing from 35 years of age, and every5 years thereafter**[(5)].**

Accordingly the aim of this study is to detect thyroid functions abnormalities in patients with type 2 diabetes mellitus and its relation to diabetic micro-vascular complications.

Subjects and Methods
The present study was conducted at the outpatient clinic of Endocrinology and metabolism of Minia University Hospital, in the period from June 2013 to December 2013. It included 100 persons who were divided into

two groups; 80 patients with type 2 DM (50 females & 30 males), their ages range from 35 to 75 years, and 20 persons (age and sex matched healthy volunteers) as control. Diagnosis of diabetes was based on the American Diabetes Association criteria[5]**.** Patients were excluded if they had history of thyroid disorders or taking medication for thyroid diseases, critically ill patients, known to have one of diabetic microvascular complications. All patients were subjected to the following: Full history taking and thorough clinical examination. Patients were considered obese if the BMI ≥ 30 kg/ m^2. All participants were subjected to the following investigations**:** fasting and postprandial glucose, HbA1C**,** Urine analysis for A/C Ratio, blood urea and creatinine**,** total Lipid profile and thyroid function tests (free T3, free T4, and TSH). All subjects had detailed fundus examination to detect diabetic retinopathy, and neurological examination for the presence of diabetic peripheral neuropathy.

Laboratory studies

Blood Sampling and Processing

Blood samples: 10ml venous blood were drawn after 10-12 hours fasting, for routine laboratory assessments:

1- Two ml of venous blood on EDTA containing tube for HbA1C**,** fasting blood glucose and postprandial glucose. Fasting glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH).

2- Two ml of venous blood for liver function tests (AST, ALT, serum albumin). Renal function test (blood urea, serum creatinine, A/C ratio) determined by spectrophotometer.

3- **Total Lipogram:**

- **Serum cholesterol and triglycerides** drawn after fasting for about 12 hours, the cut off value for cholesterol is 200 mg / dl, for triglycerides is 150 mg / dl. For HDL-cholesterol in women: 30-85 mg/dl in men: 30-70 mg/dl, for LDL is 100 mg/ dl.
- **Principle of TSH assesement:** using ELISA kits supplied from (Chemux Bio Science, Inc Company. USA), in which cut off value equal to 0.4-5.2 μIU/ml**.**
- **Free Tri iodothyronine (T3) level**: using ELISA kits supplied from (The Diagnostic Automation Inc. company) in which cut off value equal to 1.4 - 4.2 pg/ml.
- **Free Thyroxine (T4) level**: using ELISA kits supplied from (Chemux Bio Science, Inc. company, USA) in which cut off value equal to 0.65 – 1.97 ng/dL.

Diagnosis of hypothyroidism was based on low free T3, freeT4 and high TSH above the reference range. Hyperthyroidism was diagnosed by high freeT3, freeT4, and low TSH beyond the reference range. SCH was diagnosed with high TSH above the reference range with normal freeT3 and freeT4 level.

Statistical analysis

Data entry and analysis were done using software SPSS version 13, and microstats program. Graphics were done using Excel. Quantitative data were presented by mean and standard deviation, while qualitative data were presented by frequency distribution. Student t-test and Z-test used. The probability of less than 0.05 was used as a cut off point for all significant tests.

Results

- The baseline characteristicsof the 100 enrolled persons were as follow:Diabetic group included 80 patients with mean age of 56.3 ± 10.44yrs, 50 females and 30 males, with mean BMI of 30.85 ± 5.46 kg/ m^2. While control group included 20 subjects with mean age of 50.15 ± 9.98yrs, 13 females and 7 males**.**
- 54 patients were on oral treatment (sulphonyl urea and/ or metformin) while 26 patients were on mixed insulin therapy with mean duration of illness of 8.5yrs ± 7.2.
- 67 patients had peripheral neuropathy (83%), 43 diabetic patients(53.8%) had retinopathy and 39 patients(48.8%) had nephropathy.13patients had no micro-vascular complications (16.25%), while patients with combined retinopathy, neuropathy and nephropathy represent 32 patients (40 %). **(table1).**
- TSH is higher in diabetic patients than the control group (2.9 ± 2.12vs1.54 ± 0.37) respectively. These changes are statistically significant as P value = 0.037, while there is no significant difference as regard free T3 and free T4 levels as shown in **(table 2).**

- Out of 80 diabetic patients 37.5% (30 patients) have abnormal thyroid functions, distributed as follow: 17.5% (14 patients) have overt hypothyroidism, 13.75% (11 patients) have SCH, 1.25% (1 patient) has subclinical hyperthyroidism and 5% (4 patients) have overt hyperthyroidism, as shown in **(table 3).**
- The most common thyroid dysfunction among type 2 diabetic patients is hypo-thyroidism as it is present in 31.25% of diabetics patients (25 patients) divided into: 13.75% having SCH (11patients) and 17.5% having overt hypothyroidism (14 patients), while hyperthyroidism presented in 6.25% (5 patients) **(table 3).**
- Diabetic patients with thyroid dysfunction were predominantly female. As 27 (90%) out of 30 patients with thyroid dysfunctions, were females as shown in **(table 3).**
- There is a relationship between the presence of thyroid dysfunction and the incidence of micro vascular complications, as the incidence of diabetic retinopathy in diabetics with thyroid dysfunctions was higher than that in diabetics without thyroid dysfunction, 63.3% and 46% respectively. TSH is higher in diabetics with retinopathy than without retinopathy with p value (0.030). The same for diabetic nephropathy, as its incidence was 53.3% in those having thyroid dysfunctions, versus 48% in those with normal thyroid functions as shown in **(table 4 & 5).** TSH level is significantly higher in cases with nephropathy with p value (0.016) than others, while free T3 level is significantly lower with p value (0.045).
- TSH is higher in patients with neuropathy (2.96 ± 2.17vs 2.57 ± 1.91) but did not achieve statistically significant level as the p value was 0.584
- Multiple regressive analysis for TSH level revealed that DM duration is the most effective factor on TSH level as p value **0.040.**
- Logistic regressive analysis for retinopathy shows that age, duration of diabetes and TSH level considered to be risk factors for retinopathy as p value is 0.001, 0.001, 0.035 respectively **(table 6).**
- There is weak positive correlation between TSH levels and total cholesterol (r= 0.064) and LDL (r= 0.092).Also there is aweak negative correlation between free T3, free T4 and cholesterol levels (r= -0.033, r= -0.072 respectively).

Table (1): Frequency of micro-vascular complications in diabetic group

	Diabetic N=80
Retinopathy: n (%)	
Yes.	43 (53.8%)
No.	37 (46.2%)
Neuropathy: n (%)	
Yes.	67 (83.8%)
No.	13 (16.2%)
Nephropathy: n(%)	
Yes.	38 (48.8%)
No.	42 (51.2%)
Patients without complications: n (%)	13 (16.25%)
Patients with only neuropathy: n (%)	18 (22.5%)
Patients with all complications: n (%)	32 (40%)
Neuropathy + Nephropathy: n (%)	7 (8.75%)
Neuropathy + Retinopathy: n(%)	10 (12.5%)

Table (2): Thyroid functions in diabetic and control subjects

	Diabetic N=80	Control N=20	P value
TSH:			
Range.	(0.1-6.7)	(0.9-2.3)	0.037*
M ± SD.	2.9 ± 2.12	1.54 ± 0.37	
Free T3:			
Range.	(0.01-6.4)	(0.7-1.2)	0.268
M ± SD.	0.96 ± 0.95	0.89 ± 0.16	
Free T4:			
Range.	(0.01-6.7)	(0.1-1.9)	0.649
M ± SD.	0.89 ± 1.07	0.71 ± 0.48	

Table (3): Types of thyroid disorders in diabetic subjects according to gender:

	Diabetic N=80		
	Total: n(%)	**Female: n(%)**	**Males: n(%)**
Thyroid disorder: n (%)	30 (37.5%)	23(28.75%)	7 (8.75%)
Subclinical hypothyroidism.	11 (13.75%)	9 (11.25%)	2 (2.5%)
Overt hypothyroidism.	14 (17.5%)	10 (12.5%)	4 (5%)
Subclinical hyperthyroidism.	1 (1.25%)	1 (1.25%)	0
Overt hyperthyroidism.	4 (5%)	3 (3.75%)	1 (1.25%)

Table (4): Incidence of microvascular complications in diabetics with and without thyroid disorders

	Diabetic patients with thyroid disorders N=30 (37.5%)	Diabetic patients without thyroid disorders N=50 (62.5%)
Retinopathy:n (%)	19 (63.3%)	24 (46%)
Nephropathy:n (%)	16 (53.3%)	22 (48%)
Neuropathy: n (%)	27 (90%)	40 (82%)

Table (5): Comparison between thyroid functions among diabetic patients with and without retinopathy and nephropathy

	Retinopathy		
	Yes N=43	**No N=37**	**P value**
TSH:			
Range.	(0.1-6.7)	(0.1-6.1)	0.030*
M ± SD.	3.33 ± 2.15	2.39 ± 2	
T3:			
Range.	(0.19-6.4)	(0.01-1.96)	0.058
M ± SD.	0.97 ± 1.25	0.93 ± 0.41	
T4:			
Range.	(0.01-6.7)	(0.2-3.1)	0.537
M ± SD.	0.93 ± 1.34	0.85 ± 0.63	

	Nephropathy		
	Yes N=39	**No N=41**	**P value**
TSH: Range. M ± SD.	(0.5-6.5) 3.32 ± 2.02	(0.1-6.7) 2.5 ± 2.17	0.016*
T3: Range. M ± SD.	(0.19-1.4) 0.73 ± 0.33	(0.01-6.4) 1.17 ± 1.27	0.045*
T4: Range. M ± SD.	(0.01-2.1) 0.69 ± 0.46	(0.2-6.7) 1.08 ± 1.4	0.182

Table (6): Logestic regressive analysis for Retinopathy

	Retinopathy		OR (95% CI)	P value
	No (n=37)	**Yes (n=43)**		
Age	51.41 ± 10.44	60.51 ± 8.48	1.11 (1.05-1.17)	< 0.001*
Male	13 (35.1%)	12 (27.9%)	0.71 (0.28-1.85)	0.488
Female	24 (64.9%)	31 (72.1%)	1.4 (0.54-3.61)	0.488
DM duration	5.18 ± 4.96	11.34 ± 7.63	1.17 (1.07-1.28)	0.001*
BMI	31.52 ± 5.91	30.28 ± 5.04	0.96 (0.88-1.04)	0.311
FBG	170.18 ± 75.25	165.67 ± 76.14	0.99 (0.99-1.01)	0.788
PPG	280.9 ± 113.11	252.42 ± 86.3	0.99 (0.99-1.002)	0.207
Urea	40.62 ± 33.22	58.23 ± 51.95	1.01 (0.99-1.023)	0.097
Cr	1.14 ± 1.3	1.72 ± 1.6	1.4 (0.92-2.13)	0.122
HbA1c	8.06 ± 0.89	8.3 ± 1.11	1.28 (0.82-2.01)	0.278
TC	173.97 ± 52.3	167.62 ± 45.9	0.99 (0.98-1.01)	0.560
TG	176.92 ± 75.58	189.95 ± 80.48	1.01 (0.99-1.01)	0.455
HDL	35.29 ± 14.51	33.91 ± 9.52	0.99 (0.95-1.03)	0.605
LDL	108.24 ± 41.49	104.6 ± 36.57	0.99 (0.98-1.01)	0.673
TSH	2.39 ± 2	3.73 ± 3.2	1.26 (1.02-1.56)	0.035*
T3	0.93 ± 0.41	0.97 ± 1.2	1.05 (0.65-1.67)	0.855
T4	0.84 ± 0.6	0.92 ± 1.34	1.07 (0.7-1.64)	0.743

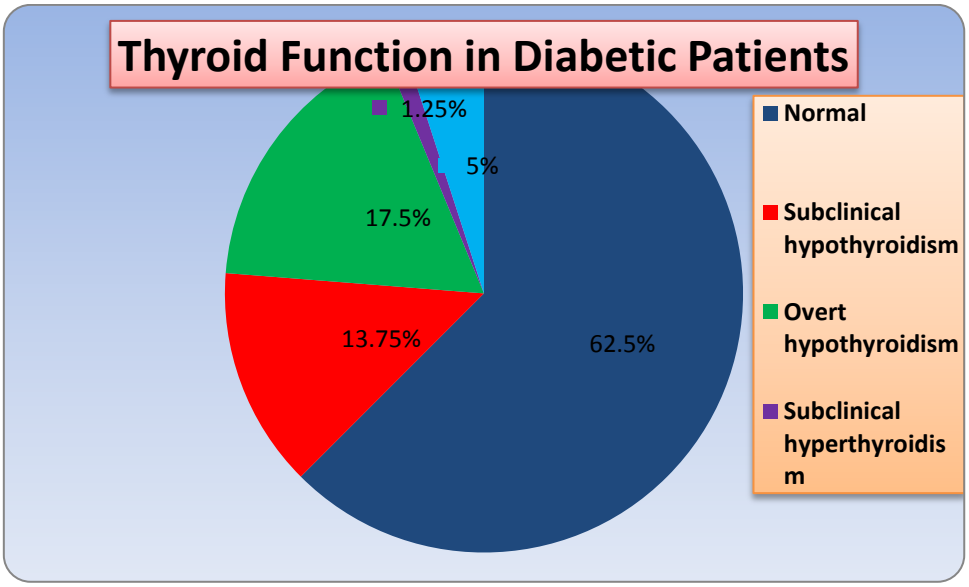

Figure (1): Types of Thyroid Disorders in Diabetic Subjects:

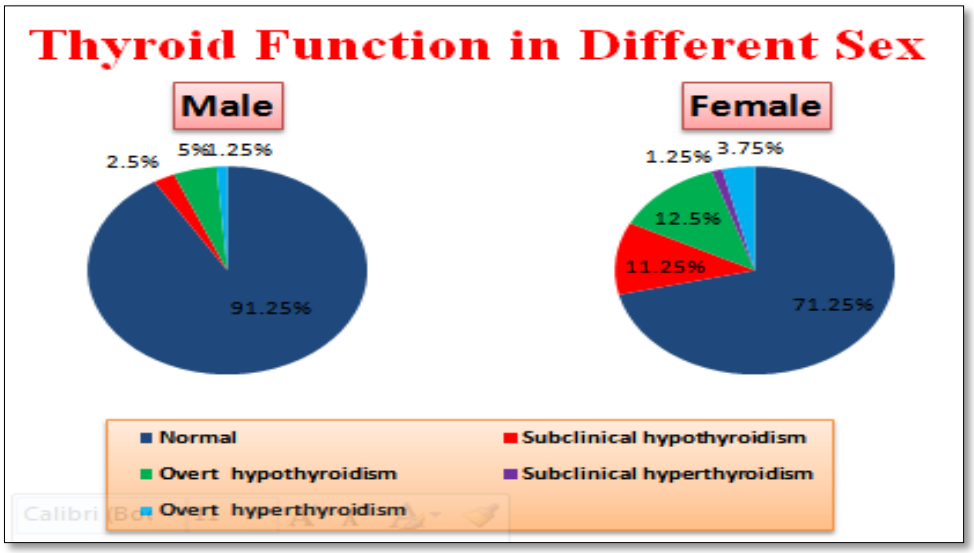

Figure (2): Types of thyroid disorders in diabetic subjects according to gender:

Discussion

The strong link between diabetes and thyroid diseases encouraged the American Diabetes Association (ADA) to propose that people with diabetes must be checked periodically for thyroid dysfunction[6]. Thyroid disease should be screened annually in diabetic patients to detect asymptomatic thyroid dysfunction, at the same time, patients with thyroid dysfunction may need to be tested for the possibility of abnormal glucose metabolism, since excessive thyroid hormones causes increased glucose production in the liver, rapid absorption of glucose through the intestine, and increased insulin resistance[7].

The present study reveals that there is higher level of TSH level, in diabetic group than control. These changes are statistically significant as P value = 0.037.The above results are consistent with a study of Singh et al., 2011[8], who found that TSH level is significantly

higher in diabetics as compared to non-diabetic subjects (as p value = <0.001).

The present study showed that 30 patients out of 80 diabetic patients (37.5%) have abnormal thyroid functions, 11 patients (13.75%) have subclinical hypothyroidism, 14 patients (17.5%) have overt hypothyroidism, one patient (1.25%) has subclinical hyperthyroidism and 4 patients (5%) have overt hyperthyroidism. The above results are in agreement with the study by Denitrost and Ranabir, 2013[9], who had studied the thyroid dysfunction in 202 type 2 diabetic patients. They noted that 31.2% of the patients had thyroid dysfunction, 16.3% have SCH, 11.4% have clinical hypothyroidism, 2% have subclinical hyperthyroidism and 1.5% has clinical hyperthyroidism.

A similar results of abnormal thyroid function in diabetics were also observed in Spain by Diez et al., 2011[10], who found 32.4% prevalence of thyroid dysfunction in type2 DM. Lower percent was observed by Papazafiropoulou et al., 2010[11], as it was only 12.3%.

The present study revealed that diabetic patients with thyroid dysfunction were predominantly females. As out of 30 patients with thyroid dysfunctions, 27 patients (90% of them) were females. It is well established that hypothyroiddism is more common in diabetic females. Autoimmune polyglandular syndrome type 2 (APS 2)which is more common in women and occurs in early to middle adulthood is characterized by autosomal dominant inheritance and presence of autoimmune Addision's disease, autoimmune thyroid disease, an immune mediated diabetes. Grave's disease and Hashimotos thyroiditis are also common in APS2[12]

This is consistent with Metab Al-Geffari et al, 2013[13], who found that female gender is a significant risk factors for different thyroid dysfunctions, as he found that thyroid dysfunctions were more common in females by a percentage of 68.6%of patients with thyroid dysfunctions.

The current study revealed that there is a relationship between the presences of thyroid dysfunction and the incidence of micro-vascular complications, as it was found that the prevalence of diabetic retinopathy in diabetics with thyroid dysfunctions was higher than that in diabetics without thyroid dysfunction, 63.3% and 46% respectively. The same for diabetic nephropathy, as its incidence was 53.3% in those having thyroid dysfunctions, while it was 48% in those with normal thyroid functions. It is a very well-known fact that the endothelium plays a major role in vascular tone, vascular homeostasis, vascular smooth muscle cell proliferation and thrombosis and thrombolysis balance through the production of a large number of vasoactive chemicals, growth modulators and other factors that mediate these functions [14].

Thyroid function contributes to normal retinal vascular density. Further, hypothyroidism can play a permissive role in the development of retinal neo-vascularization. Infants born very prematurely (27 weeks) were more likely to have low thyroxin levels indicating an abnormal function of hypothalamo-pituitary-thyroid axis [15]. Premature infants with low serum thyroxin were at risk of retinopathy of prematurity[16]. In addition hypothyroidism increased retinal vascular permeability in rats [17].

SCH is associated with diabetic retinopathy in type 2diabetic patients. There is also an association between level of TSH and the stage of diabetic retinopathy in type 2 diabetics with subclinical hypothyroidism[18].

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