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Thyroid dysfunction among type 1 diabetic patients; the time for induction of screening strategies by family physician

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Abstract
Background: Diabetes mellitus and thyroid dysfunctions are the most two common endocrinopathies seen in family practice. Type 1 diabetes mellitus (T1DM) is frequently associated with autoimmune thyroid diseases (ATD). Genetic susceptibility to autoantibodies formation in ATD and T1DM has been described with varying frequencies, but there is still debate about the situation in the Saudi Arabia.
Objectives: The main objective is health promotion of type 1 diabetic patients (T1DPs) assuring a better quality of their life. The specific objectives were to determine the prevalence of thyroid dysfunction among T1DPs, to clarify the effect of one on the other, and to assess the need for screening of thyroid dysfunction among T1DPs.
Methods: A cross-sectional comparative study was conducted on all eligible T1DPs (No 310) who later were assigned as a case group and 320 non-diabetics with matched age, sex and socioeconomic criteria as a control group after their consent. They were subjected to full history taking, thorough clinical examination, and laboratory estimation of TSH, free T4, freeT3 and thyroid peroxidase antibodies (TPO-Abs). The case group was further subjected to glycosylated hemoglobin and lipid profile as indicators of diabetes control and dyslipidemia.
Results: Prevalence of thyroid disorders was significantly higher among T1DPs constituted 21.9% versus 9.7% in non-diabetics. Most cases of thyroid dysfunction (67.7%) were hypothyroidism. Type1diabetes and thyroid dysfunctions were significantly affected by each other ($P<0.05$). Furthermore, thyroid dysfunction may significantly amplify the diabetic complications through inter-relationships with dyslipidemia.
Conclusions: The family physician is in a prime position for conduction of a systematic screening approach for thyroid dysfunctions among T1DPs assuring adequately controlled T1DM with a high quality of life.

Keywords: thyroid dysfunction, hypothyroidism, hyperthyroidism, dyslipidemia, endocrinopathies, hypoglycemia, hyperglycemia

1. Introduction

Diabetes and thyroid diseases are the most two common endocrinopathies seen in clinical practice [1]. Diabetes mellitus (DM) is a major public health problem in the current era. Epidemiological studies reported that 195 million people currently suffer from DM which is expected to increase to 330 up to 500 million in the year 2030 [2].The prevalence of thyroid dysfunction in general population was estimated to be 6.6%, that is higher in diabetes because of the increased age of diabetic patients as well as the autoimmune link. The association between type 1 diabetes and autoimmune thyroid disorders (AITD) was firstly described in the early 1960s. Chronic AITD is characterized by a presence of thyroid-specific auto-antibodies in the serum with varying degrees of thyroid dysfunction either hyperthyroid, euthyroid or hypothyroid. Thyroid peroxidase antibodies (TPO-Abs) are the most sensitive and antigen-specific thyroid auto-antibodies [1]. The frequency of positive thyroid antibodies in adolescents with type 1 diabetes varies considerably from 3 to 50% in different countries [3]. As insulin and thyroid hormones being intimately involved in the cellular metabolism thus excess or deficit of either of these hormones could result in functional derangement of the other [4].

2. Objectives of the Study

The main objective was health promotion of diabetic patients assuring a better quality of life and the specific objectives were to determine the prevalence of thyroid dysfunction in type 1 diabetic patients (T1DPs), to clarify the effect of one on the other, and to decide whether it is essential or not to implement a strategy for screening of thyroid dysfunctions in type 1 diabetic patients.

3. Subjects & Methods

A cross-sectional comparative study to estimate the prevalence of thyroid dysfunctions among type1 diabetic patients. The diabetic patients confirmed to had a thyroid dysfunction were compared with those haven't the illness for further study of the problem and its risk factors. The study was conducted in Al-Zaher primary health care center, Makkah Al-Mukaramah, Saudi Arabia. The study was

conducted during the period from the first of January to the end of April 2015.

Population of the study
All registered T1DPs with a matched control group were eligible for the study.

Exclusion criteria
Any participants had; acute illnesses as rheumatic fever, chronic diseases as nephritis, cancer, pregnancy or those who were receiving radiations, taking chemotherapy or drugs affecting thyroid function.

Ethical issues
The study was approved by the ethical committee of the faculty of medicine.

Procedure of the study
All registered T1DPs (No 340), were invited to share in the study. After exclusion of 30 cases (18 refused, 8 didn't fulfill the inclusion and exclusion criteria, and 4 were dropped out during the study) 310 T1DPs were completed the study as a case group together with 320 of non-diabetics with matched age, sex and socioeconomic criteria as a control group. Both groups were subjected to:

- Full history taking including ; personal data such as age, sex….etc, key manifestations of diabetes such as polyuria, polyphagia, thirst, weight loss,……..etc and family history of diabetes, autoimmune disorders, thyroid dysfunctions…etc.
- Thorough clinical examinations by the researchers with a special emphasis on the manifestations and complications of both thyroid dysfunction and diabetes mellitus.
- Laboratory investigations including:
  1) Quantitative serum determination of TSH, free T3 and free T4.
  2) Estimation of thyroid auto-antibodies using enzyme-linked immune-sorbent assay (ELISA) for detection of thyroid peroxidase antibody (TPO-AB)
- The case group was further subjected to laboratory assessment of:
  1) Glycosylated hemoglobin (HbA1c).
  2) Lipid profile (Total cholesterol, high-density lipoprotein-HDLP, low-density lipoprotein- LDL and triglycerides).
- Patients were diagnosed to have
  1) 1-Overt hypothyroidism when TSH >4.2 mU/I and free T4<12pmol/I and/or free T3 <2.8-pmol/I
  2) 2-Overt hyperthyroidism when TSH<0.27mU/I and free T4>22pmol/I and/or free T3 >7.1-pmol/I
  3) 3-Subclinical hypothyroidism when TSH >4.2 mU/I with normal free T4 and free T3
  4) 4-Subclinical hyperthyroidism when TSH <0.27 mU/I with normal free T4 and free T3

4. Statistical Analysis
The results were collected, tabulated and statistically analyzed using a personal computer with SPSS (Statistical Program for Social Sciences) software program, version 18 under windows. Quantitative data were expressed as the mean and standard deviation ($\chi \pm SD$) and analyzed by Student's t-test. Qualitative data were expressed as number and percentage (No. and %) and analyzed by Chi- square test (χ^2). The level of significance was set at a P-value < 0.05.

5. Results and Discussion
Diabetes mellitus and thyroid dysfunctions are the most two common endocrinopathies seen in family practice. Type1 Diabetes Mellitus (T1DM) is frequently associated with autoimmune thyroid diseases (ATD). Genetic susceptibility to auto-antibodies formation in T1DM has been described with varying frequencies, but there is still debate about the situation in Saudi Arabia**.** In the present study, there was a significant higher prevalence of thyroid dysfunction among T1DPs in comparison to control group (21.9% versus 9.7%). This was in concordance with Bergesio *et al*., [6] who found that, patients with immune-mediated T1D are also prone to autoimmune thyroid diseases. In Arab countries, a figure of 8% was reported from Saudi Arabia [7]. A possible explanation for this association could be that, the same susceptibility and genotypes are involved in the etiopathogenesis of these diseases. In the present study, hypothyroidism was significantly the highest prevalent type of thyroid dysfunction among T1DPs.

In this study, hypothyroidism was the commonest type of thyroid dysfunction among T1DPs (67.7%) in comparison to hyperthyroidism in control group (61.3%). This was in concordance with the study of Gemma *et al*. [8] in Spain on 176 T1DPs between 1987- 2004; who found that, eighteen of these patients (14.2%) developed thyroid dysfunction during their follow-up where primary hypothyroidism occurred in 17 cases and hyperthyroidism in only one case. Also, this was in concordance with the findings of Ban and Tomer [9] who reported that the majority of cases (80%) occurred as a subclinical and clinical hypothyroidism (50% vs. 30%). In this study, 10.3% vs. 89.7% of diabetic patients with thyroid dysfunction; in comparison, to12.9% vs. 87.1% in control group were males and females respectively and this difference was statistically insignificant. This result was in concordance with the findings of Colorado study [10], where 25,862 were screened for thyroid diseases. The study has documented a higher prevalence of thyroid disease in women than men, with prevalence rates ranging from 4% to 21%, vs. 2.8% to 16% respectively. Also, the results were agreed with the finding of Souza *et al.* [11], who studied the prevalence of thyroid dysfunction among Brazilian adolescent regarding their gender found that the prevalence was higher among females with T1D as they significantly were predisposed to develop autoimmune thyroiditis. At the age of 18 years, almost every fifth girl with T1D was diagnosed as having an autoimmune thyroiditis requiring treatment with L-thyroxin [12].

In this study, there was an insignificant difference between both groups as regard age and duration of diabetes. We also found a tendency for anti-TPO to occur irrespective of either age or duration of the disease. This was against the study of Kordonouri *et al*., [13] who found that, T1DPs with thyroid dysfunction were significantly older and had a longer duration of diabetes than those without thyroid dysfunction. However, this result disagreed with that of Verge *et al*. [14].

In our study, family history of thyroid dysfunction was positive in 66.2% of diabetic patients having thyroid dysfunction versus 31.8% of diabetics without thyroid dysfunction, this difference was statistically significant. This result was in concordance with the study of Chubb *et al*., [15]

who did a cross-sectional study on 3,128 men and 4,821 women, aged 35-56 years and found that, 50% were having a family history of thyroid dysfunction.

In our study, family history of autoimmune disorders was positive in 75%of diabetic patients with thyroid dysfunction versus 11.2% in those without thyroid dysfunction, this difference was statistically significant. This result was in concordance with Vrbikova *et al*. [16] who stated that, thyroid auto-antibodies are found in 20–30% of patients with T1D, and with the study of Payami *et al*., [17] who found that, the prevalence of autoimmune thyroiditis (AIT) in families with autoimmune disorders is up to 30 times more than in the general population attributed to genetic background.

In this study, 47.1%, 48.5% and 26.5% of diabetic patients with thyroid dysfunction in comparison to 26.7%, 30.6% and 9.1% of diabetic patients without thyroid dysfunction were smokers, obese and have an auto-immune disorders respectively the difference was statistically significant. This was in concordance with the study of Vrbikova *et al*., [16] who found that autoimmune thyroiditis (AIT) is a group of inflammatory thyroid disorders that are associated with either hyperthyroid, euthyroid or hypothyroid state. Autoimmunity to thyroid antigens leads to two distinct pathogenic processes with opposing clinical outcomes; hypothyroidism in Hashimoto's thyroiditis and hyperthyroidism in Graves' disease. According to most studies, it may take years for patients with positive autoimmune serology to develop thyroid disease.

In this study diabetes was less controlled when associated with thyroid dysfunction detected by glycosylated hemoglobin (HbA1c). In a study by Franzese [18], it was founded that, thyroid dysfunction can affect the metabolic control in T1D, and some studies have shown a higher severity of diabetes when it is associated with AITD, however, a study by Glastras [19] found no association.

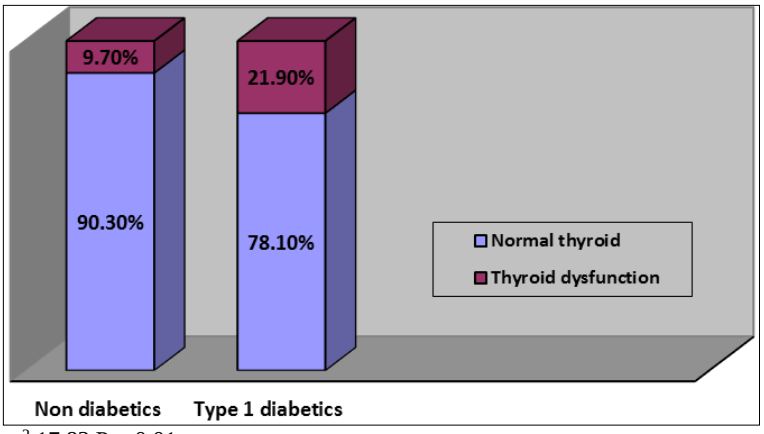
It has been suggested that, the co-existence of hypothyroidism even the subclinical type (slightly elevated TSH without changes of T3 and T4 levels) with DM might cause disturbances in its metabolic control; i.e. higher frequency of symptomatic hypoglycemia. This finding can be explained on the basis of the physiological effects of thyroid hormones on carbohydrate metabolism which are well known as thyroid hormones stimulate glucose intestinal absorption, glycogenolysis, and hepatic insulin catabolism. These mechanisms have a hyperglycemic effect and subtle changes in thyroid hormones levels might interfere with these actions, thereby increasing the risk of hypoglycemia [20]. Overt hypothyroidism can thus cause prolonged severe hypoglycemia and by causing secondary hypercholesterolemia it can also enhance the development of macroangiopathic complications. When diabetes occurs in euthyroid individuals, it results in altered thyroid function test. On the other hand, when hyperthyroidism occurs in the setting of euglycemia, 2-3% of these individuals may become diabetic [5]. Thyroid hormones, tri-iodothyronine (T3) and tetra-iodothyronine (T4) are insulin antagonists, being diabetogenic specially with high level on the other hand absence of these hormones inhibits the development of diabetes mellitus [5].

In this study, there were 39.7% and 61.8% of diabetic patients with thyroid dysfunction in comparison to 20.2% and 31.5% of diabetic patients without thyroid dysfunction had Macro- and micro-vascular complications respectively with a highly significant difference. This result was in concordance with the study of Ahren *et al*., [21] who found that, hypothyroidism is accompanied by a variety of abnormalities in plasma lipid metabolism, including elevated triglyceride and low-density lipoprotein (LDL) cholesterol concentrations. Even sub-clinical hypothyroidism can exacerbate co-existing dyslipidemia and further increase the risk of cardiovascular diseases. Adequate thyroxin replacement will reverse the lipid abnormalities [22].

6. Tables and Figures

Table 1: Socio-demographic criteria of studied groups

Socioeconomic items \ Studied groups		Diabetic group (No. 310)		Control group (No. 320)		Test	P
Age		44 ± 13.5		42 ± 12.7		1.58	> 0.05
		No	**%**	**No**	**%**		
Sex	Male	165	53.2	155	48.4	1.44	> 0.05
	Female	145	46.8	165	51.6		
Occupation	laborer	119	38.4	114	35.6	0.55	> 0.05
	Skilled	89	28.7	94	29.4		
	Employee	102	32.9	112	35.0		
Education	Illiterate	124	40.0	123	38.5	3.22	> 0.05
	Basic	94	30.3	82	25.6		
	High	92	29.7	115	35.9		
Socioeconomic level	Low	122	39.3	131	40.9	0.30	> 0.05
	Moderate	101	32.6	98	30.6		
	High	87	28.1	91	28.5		
Residency	Urban	155	50.0	159	49.7	0.01	> 0.05
	Rural	155	50.0	161	50.3		



χ^2 17.83 P < 0.01

Fig 1: Prevalence of thyroid dysfunction among type 1 diabetics and non-diabetic participants

Table 2: Serum thyroid hormone levels in diabetic and non-diabetic subjects.

Thyroid hormones	Study groups		t test	P value
	Diabetic patients	Non-diabetic subjects		
TSH (mIU/ml)	1.98 ± 1.01	2.44 ± 1.23	3.14	<0.05
FT4 (ng/ml)	1.68 ± 0.85	0.26 ± 0.71	12.55	<0.001
FT3 (pg/ml)	3.87 ± 1.77	4.6 ± 0.1	3.40	<0.001
TPO-Abs (units)	0.41±0.2	0.85± 0.16	16.64	<0.001

Table 3: Distribution of types of thyroid dysfunction in both diabetics and non-diabetic groups.

Studied groups / Thyroid state	Thyroid Dysfunction				χ^2	P value
	In Diabetics group (No. 68)		In Non-Diabetic group (No. 31)			
	No.	%	No.	%		
Subclinical Hypothyriodism	20	29.4	5	16.1		
Clinical Hypothyroidism	36	52.9	7	22.6		
Total	**56**	**82.3**	**12**	**38.7**		
Subclinical Hyperthyriodism	8	11.8	12	38.7		
Clinical Hyperthyriodism	4	5.9	7	22.6		
Total	**12**	**17.7**	**19**	**61.3**		
Total	68	100.0	31	100.0	19.00	< 0.001

Table 4: Risk factors of thyroid dysfunction among type 1 diabetic participants.

Risk factors / Studied groups		Diabetic cases				χ^2	P value
		With thyroid dysfunction (No.68)		Without thyroid dysfunction (No.232)			
		No	%	No	%		
Family history of thyroid disorders	Positive	45	66.2	76	32.8	4.04	< 0.01
	Negative	23	33.8	156	67.2		
	Total	68	100.0	242	100.0		
Family history of autoimmune disorders	Positive	51	75.0	26	11,2	112.17	< 0.01
	Negative	17	25.0	206	88.8		
	Total	68	100.0	232	100.0		
Risk factors of thyroid dysfunction	Smoking	32	47.1	62	26.7	2.44	> 0.05
	Auto-immune disorders	18	26.5	21	9.1	45.2	< 0.01
Duration of disease in years (Mean ± SD)		9 ± 5.6		8± 4.8		t test	P
						1.45	> 0.05
BMI (Mean ± SD)		25.7 ± 4.1		23.7 ± 2.7		4.72	< 0.01

Table 5: Correlation between different variables in type one diabetics

Variable	HbA1C	TSH	Anti TPO
HA1C	1	-0.04	0.07
TSH	-0.04	1	*0.23
Anti TPO	-0.07	*0.23	1

*P <0.05

Table 6: Comparison between diabetics with and without thyroid dysfunction as regard indicators of diabetic control

Studied groups / Indicators of diabetic control	Diabetic cases				t test	P value
	With thyroid dysfunction (No.68)		Without thyroid dysfunction (No.232)			
Lipid Profile	(Mean (mg/dl) ± SD)		(Mean (mg/dl) ± SD)			
Total cholesterol	187± 44.6		138± 49.8		7.38	< 0.001
HDL cholesterol	43.6± 24.8		36.2± 23.4		2.27	< 0.05
LDL cholesterol	144.3± 43.6		116.3± 83.6		2.66	< 0.05
Triglycerides	222±114.6		187±118.6		2.17	< 0.05
Glycosylated HbA1C	**No.**	**%**	**No.**	**%**	χ^2	
< 6	12	17.6	121	52.2		
6-8	22	32.4	66	28.4	33.10	< 0.01
>8	34	50.0	45	19.4		
Uncontrolled DM					χ^2	Odds ratio
Frequent Hypoglycemic comas	17	25.0	31	13.4	5.30*	2.16
Frequent Hyperglycemic comas	24	35.3	44	18.9	8.00*	2.33
Diabetic complications						
Macro-vascular complications	27	39.7	47	20.2	10.70*	2.59
Micro-vascular complications	42	61.8	73	31.5	20.42*	3.52

** P<0.01

7. Conclusion

Type one diabetic patients have higher prevalence of thyroid dysfunction with positive thyroid auto-antibodies among the diabetics than non-diabetic participants

8. Recommendations

- As screening for thyroid dysfunction in Egypt is justified only for neonates; a case can be made to extend thyroid screening to type 1diabetic patients.
- Family physician is in a prime position for conduction of a systematic approach for screening of thyroid dysfunctions among T1DPs.
- Study the cost-effectiveness of such screening is needed.
- As, we could not demonstrate any effect of the duration of diabetes on the prevalence of thyroid dysfunction, so, screening should start early once the diabetes is diagnosed.
- For screening purposes, detection of auto-antibodies is the most sensitive in diagnosing preclinical endocrine dysfunction

Genetic predisposing factors responsible for this interesting phenomenon need to be further investigated.

9. References

1. Sostree S, Reyes M. Sonographic diagnosis and grading of Hashimoto's thyroiditis. J Endocrinol Invest. 2006; 14:115-121.
2. Alberti K, Zimmet P. Diagnosis and classification of diabetes, provisional report of a WHO Consultation. Diabet. Med 2006; 15:5395-42.
3. American Diabetes Association. Screening and detection of diabetic peripheral neuropathy. Diabetes care. 2008; 26:331-334.
4. Donckier J. Endocrine diseases and diabetes. In: Text book of Diabetes mellitus. Pickup JC, Williams G (eds), Blackwell Publishing Company, Chichester, 2005; 27(1):27-25.
5. Sara N, Mohammed O, Abd Elrahim M, Inaam N. The prevalence of thyroid peroxidaseauto-antibodies in Sudanese participants with type 1 diabetes mellitus, Khartoum Medical Journal. 2010; 3(1):381-384.
6. Bergesio F, Bandini S, Cresci B, Monzani G, Rotela C, Conti A, *et al*. Hyperthyroidism: Is it really the major factor affecting glucose tolerance in ureamia. Electrolyte Metab. 2003; 22(1-3):187-91.
7. Abdullah M, Bahakim H, Gad Al Rab M, Halim K, Salman H, Abanamy A. Antithyroid and Other Organ-specific Antibodies in Saudi Arab Diabetic and Normal Participants. Diabetic Medicine. 1990; 7:50-52.
8. Ismael C, Gemma C, José R, Didac M. Thyroid autoimmunity at onset of type 1 diabetes mellitus as predictor of thyroid dysfunction. Diabetes Care; ADA, 2007.
9. Ban Y, Tomer Y. Genetic susceptibility in thyroid autoimmunity. Pediatr Endocrinol Rev. 2007; 3:20-32.
10. Carnaris G, Manowitz N, Mayor G, Ridgway E. The Colorado Thyroid Disease Prevalence Study. Arch intern Med. 2004; 160:526-534
11. Souza O, Diehl La, Carleto L. Prevalence of thyroid autoimmunity in a group of patients with type 1 diabetes mellitus in Londrina, PR. Arq Bras Endocrinol Metabol. 2005; 49:228-233.
12. Vanderpump M, Tunbridge W. Epidemiology and prevention of clinical and subclinical hypothyroidism. Thyroid. 2002; 12:839-47.
13. Kordonouri O, Hartmann R, Deiss D, Wilms M, Grüters-Kieslich A. Natural course of autoimmune thyroiditis in type 1 diabetes: Association with gender, age, diabetes duration and puberty. Arch Dis Child. 2005; 90:411-414.
14. Verge C, howard N, Rowley M. Antiglutamate decarboxylase and other antibodies at the onset of childhood type 1 diabetes: a population-based study. Diabetologia. 1994; 37:1113-1120.
15. Chubb S, Davis W, Inman Z, Davis T. Prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes: the Fremantle Diabetes Study. Clin Endocrinol (Oxf). 2005; 62:480-486.
16. Vrbikova B, Bendlova K, Sterzl M. Differences in type I diabetes mellitus of young adults with and without thyroid autoimmunity, Exp. Clin. Endocrinol. Diabetes. 2005; 113:404-408.

17. Payam H, Joe S, Thomson G. Autoimmune thyroid disease in type 1 diabetic families. Genet. Epidemiol vol. 1989; 6:137-141.
18. Franzese A, Buono P, Mascolo M, Leo A, Valerio G. Thyroid autoimmunity starting during the course of type 1 diabetes denotes a subgroup of participants with more severe diabetes. Diabetes Care. 2000; 23:1201-1202.
19. Glastras S, Craig M, Verge C, Chan A, Cusumano J, Donaghue K. The role of autoimmunity at diagnosis of type 1 diabetes in the development of thyroid and celiac disease and microvascular complications. Diabetes Care. 2005; 28:2170-2175.
20. Mohn A, DI Michele S, DI Luzio R, Tumini S. The effect of subclinical hypothyroidism on metabolic control in participants and adolescents with Type 1 diabetes mellitus. Diabet Med. 2002; 19:70-73.
21. Ahren B, Lundquist I, Hedner P, Valdemassan S, Scheroten B. Glucose tolerance and insulin and c peptide responses after various insulin secretions stimuli in hyperthyroid and hypothyroid subjects before and after treatment. Diab. Res. Clin. Practice. 2004; 2:95-103.
22. Randin J, Tappy L, Scazziga B, Jequier E, Felber J. Insulin sensitivity and exogenous insulin clearance in Grave's disease. Measurements by the glucose clamp technique and continuous glucose calorimetry. Diabetes, 2006; 35:178-81.