Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan

Abdel-Rahman M. Radaideh, *MD,* ***Mohamad K. Nusier,*** *MD, PhD,* ***Fawaz L. Amari,*** *MD, FRCP,*
Anwar E. Bateiha, *MD, PhD,* ***Mohammed S. El-Khateeb,*** *PhD,* ***Abeer S. Naser,*** *BCs,* ***Kamel M. Ajlouni,*** *FACP, FACE.*

ABSTRACT

Objective: To investigate the prevalence of thyroid dysfunction and autoimmunity in type 2 diabetic patients.

Methods: The study was conducted at the National Center for Diabetes, Endocrinology and Genetics, Jordan University Hospital, Amman, Jordan, between March 2000 and September 2000. A group of 908 type 2 diabetic patients (T2DM) were recruited in the study and underwent investigations for thyroid functions; free thyroxine (FT_4), free tri-iodothyronine (FT_3) and thyroid stimulating hormone (TSH). Six hundred had performed thyroid autoantibodies, thyroid peroxidase antibodies (TPOab) or antimicrosomal antibodies (AMA) and thyroglobulin antibodies (Tgab). They were compared with 304 non-diabetics, of those 282 had performed thyroid antibodies.

Results: Fifty-three (5.9%) of diabetic patients were known to have thyroid disease. As a direct result of screening, new thyroid disease cases were diagnosed in 6.6% of the patients. Thus, the overall prevalence of thyroid disease was found to be 12.5%. The most common was subclinical hypothyroidism (4.1%). In the control group, the prevalence of thyroid disease was 6.6%. The most common was subclinical hypothyroidism (5%). There was a significant difference between diabetics and control subjects p=0.0064. Positive TPOab was found in 8.3% of T2DM patients (N=600) versus 10.3% in the control group (N=282) p=0.412. Positivity for both TPOab and Tgab was found to be 2.5% of T2DM versus 6% of the control subjects p=0.0155.

Conclusion: This study suggests that diabetic patients should be screened for asymptomatic thyroid dysfunction.

Saudi Med J 2004; Vol. 25 (8): 1046-1050

Thyroid diseases are common in the general population[1] and modern assays provide a reliable and inexpensive method of assessing thyroid function.[2] Screening for thyroid dysfunction is indicated in certain high-risk groups, such as neonates[3] and the elderly,[4] and this may be justified in diabetic patients who have higher prevalence of thyroid disorders compared with the normal population.[5,6] Since the prevalence of diabetes mellitus (DM) is high in Jordan,[7] this study was aimed to determine the prevalence of thyroid disease and thyroid autoimmunity in Jordanian patients with type 2 diabetes mellitus (T2DM) attending the diabetic clinic in the National Center for Diabetes, Endocrinology and Genetics. A similar study describing the prevalence of thyroid dysfunction in patients with type 1 diabetes mellitus has been reported.[8]

From the National Center of Diabetes, Endocrinology and Genetics (Radaideh, El-Khateeb, Naser, Ajlouni), Department of Biochemistry and Molecular Biology (Nusier, Amari) and the Department of Public Health (Bateiha), Jordan University of Science and Technology, School of Medicine, Irbid, *Jordan*.

Received 14th December 2003. Accepted for publication in final form 13th March 2004.

Address correspondence and reprint request to: Prof. Kamel Ajlouni, National Center of Diabetes, Endocrinology and Genetics, PO Box 13165, Amman 11942, *Jordan*. Tel. +962 (6) 5353374. Fax. +962 (6) 5353376. E- mail: ajlouni@ju.edu.jo

Methods. The criteria for diagnosis of type 2 diabetes were the American Diabetic Association criteria; fasting blood sugar of 126 mg/dl, random blood sugar 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 with diseases that may affect thyroid function were excluded. The patients on medications that can affect thyroid function were also excluded. All type 2 diabetic patients who were treated at the National Center for Diabetes, Endocrinology and Genetics, Jordan University Hospital, Amman, Jordan, between March 2000 and September 2000 were selected. The number of patients randomized for the study was 1000, 92 were excluded according to the exclusion criteria, the data of the remaining 908 was analyzed. All patients were assessed for signs and symptoms related to thyroid dysfunction. A random sample from 908 adult T2DM patients was recruited for this study, 480 females (52.9%) and 428 males (47.1%). The mean age ± standard deviation (SD) of the investigated patient was 50.4 ± 9.8, and the age range was 26-85 years.

A group of 304 subjects, 174 (57.2%) females and 130 (42.8%) males, were included as a control group. This group was neither diabetics nor known to have any endocrine disorder nor any other disease that may affect the thyroid function. The mean age ± SD of the control group was 49.4 ± 14.2 and the age range was 30-80 years. Venous blood samples were withdrawn and assayed for thyroid function such as free thyroxine (FT_4), free tri-iodothyronine (FT_3), thyroid stimulating hormone (TSH), thyroid autoantibodies (Tab), anti-thyroid peroxidase (TPOab), or antimicrosomal antibodies (AMA), thyroglobulin antibodies (Tgab) and hemoglobin A_{1C} (HbA_{1C}). Tests were either directly analyzed from venous blood samples or serum was frozen at -20^{0}C until analysis. Abnormal thyroid function tests were carried out in duplicate for each patient. All participants were given informed consent and the study was approved by the ethical committee of the center. Serum FT_4 (normal range = 9.1-23.8 Pmol/L), serum FT_3 (normal range = 2.85-5.44 Pmol/L) and serum TSH (normal range = 0.40-5.0 mU/L) were determined by enzyme-linked immunosorbent assay (ELISA) method (Abbott Lab, USA). Serum TPOab (normal range <10U/L), serum Tgab (normal range <100 U/L) were analyzed by Immunoradiometric assay (IRMA) (Diasorin, Italy); and AMA (normal range <15U/L) were also analyzed by ELISA (Diasorin, Italy). Hemoglobin A_{1C} (HbA_{1C}) (normal range 4.2-6.2%) was assayed using a high performance liquid chromatography (HPLC). All assays were performed in clinical laboratories of the Center. The following guidelines for detection of thyroid dysfunction were considered:[9] 1) Normal - when both FT_4 and TSH were within the normal range. 2) Overt hypothyroidism - when TSH is more than 10 mU/L and FT_4 is less than the normal value. 3) Overt hyperthyroidism - when TSH is less than 0.1 mU/L and FT_4 or FT_3 is more than the normal values. 4) Subclinical hypothyroidism - when TSH is more than 5mU/L and FT_4 is within the normal range. 5) Subclinical hyperthyroidism - when TSH is less than 0.1 mU/L and FT_3 and FT_4 are within the normal range. Antibodies were considered positive if they were above the normal range.

Data were analyzed using EPI Info version 6. Results were expressed as mean ± SD and range. The prevalence of thyroid dysfunction among T2DM patients and controls were compared using Chi-square test. Student t-test was used to compare the 2 groups with respect to continuous variables. The $p<0.05$ were considered significant.

Results. Clinical characteristics and demographic features of the whole cohort are seen in **Table 1**. Fifty-three T2DM patients (**Table 2**) (5.9%) had a previous thyroid disease; hypothyroidism was identified in 45 patients (13 post-thyroidectomy, 25 with primary hypothyroidism, 6 post-radioactive-iodine [post-RAI] treatment for hyperthyroidism and one with panhypopituitarism). Three patients have hyperthyroidism (Grave's disease): 2 of them are on neomercazole (NMZ) treatment and one was still having active disease post-RAI treatment. Five euthyroid female patients: 3 had thyroidectomy for large goitre, one post-RAI treatment and one post NMZ treatment for hyperthyroidism. The

Table 1 - Characteristics of diabetic patients and control group.

Characteristics	**Diabetics N=908** n (%)	**Controls N=304** n (%)	***p* value**
Sex			
Female	480 (52.9)	174 (57.2)	0.21
Male	428 (47.1)	130 (42.8)	0.21
Mean age ± SD (years)	50.8 ± 9.8	49.4 ± 14.2	0.056
Duration of T2DM ± SD (years)	8.3 ± 6.6	NA	
Hemoglobin A_{1C}	6.6 ± 2.2	NA	
Treatment			
Oral	541 (59.6)	NA	
Insulin	200 (22)	NA	
Insulin + Oral	110 (12.1)	NA	
Diet	57 (6.3)	NA	

T2DM - type 2 diabetes mellitus, NA - not applicable,

prevalence of established thyroid disease was higher in female comprised of 41 (8.5%) patients than in male with 12 (2.8%) patients. Sixty new cases of thyroid disease were diagnosed in the studied T2DM patients (**Table 2**). The prevalence of newly discovered thyroid disease in T2DM patients was 6.6%. Primary hypothyroidism was diagnosed in 11 cases, subclinical hypothyroidism in 37 cases, hyperthyroidism in one case and subclinical hyperthyroidism in 11 patients. Female patients have a higher prevalence comprised of 43 (9%) patients than male with 17 (3.9%) p=0.03. The prevalence peaked in the fifth and sixth decades of age (**Table 3**). The overall prevalence of known and newly discovered disease in T2DM patients was 12.5% with a higher prevalence in female comprised of 85 (17.5%) than in male patients with 28 (6.5%) p<0.00006. In the age and sex matched control group, a new diagnosis of thyroid disease was made in 20 subjects (**Table 2**), with a prevalence of 6.6%. Hypothyroidism was diagnosed in 3 subjects: 2 females and one male. Subclinical hypothyroidism was diagnosed in 15 subjects: 9 females and 6 males. Hyperthyroidism was diagnosed in one female and subclinical hyperthyroidism in one female. Female controls were found to have a higher prevalence of thyroid disease comprised of 13 (7.5%) than males 7 (5.4%) p=0.6. Thyroid disease occurred across a wide spectrum of age in the control group (**Table 3**). There was a significant difference between thyroid dysfunction in T2DM patients 12.5% versus 6.6% in control subjects p=0.0064 (**Table 2**).

Table 2 - Thyroid disease in 908 type 2 diabetes mellitus (T2DM) patients and in 304 control subjects.

Characteristics	Hypothyroidism n (%)	Subclinical hypothyroidism n (%)	Hyperthyroidism n (%)	Subclinical hyperthyroidism n (%)	Euthyroidism n (%)	Total n (%)
T2DM patients (N=908)						
Male	16 (1.8)*	9 (1)	2 (1)	1 (0.1)	-	28 (3.1)
Female	40 (4.4)*	28 (3)	2 (3)	10 (1.1)	5 (0.6)	85 (9.4)
p value	0.006	0.007	0.64	0.025	0.04	<0.00006
Control group (N=304)						
Male	1 (0.3)	6 (2)	- (2)†	- -	- -	7 (2.3)
Female	2 (0.6)	9 (3)	1 (3)†	1 (0.3)	- -	13 (4.3)
p value	0.6	0.960	0.570	0.57		0.62
Total *p* value	**0.0005**	**0.63**	**0.63**	**0.15**	**0.23**	**0.0064**

*35 female and 10 male patients are known cases of hypothyroidism. †one female and 2 male patients are known cases of hyperthyroidism.

Table 3 - Age distribution of thyroid diseases in type 2 diabetes mellitus patients and control group.

Thyroid disfunction	20-29		30-39		40-49		50-59		60-69		≥70	
	DM	Control	DM	Control	DM	Control	DM	Control	DM	Control	DM	Control
Euthyroid												
Male	2	0	14	25	75*	37	147	29	127†	21	34	10
Female	3	0	24	53	80	43	151	28	116	23	29	19
Hyperthyroidism												
Male	0	0	0	0	2	0	1	0	1	0	0	0
Female	0	0	0	2	2	0	2	0	3	0	2	0
Hypothyroidism												
Male	0	0	2	0	7	4	7	0	6	1	3	3
Female	0	0	2	4	11	1	27	3	20	1	8	1
Total	**5**	**0**	**42**	**84**	**177**	**85**	**335**	**60**	**273**	**46**	**76**	**33**

*2 patients has euthyroidism (one post-radioactive-iodine, †one post-neomercazole treatment). †3 patient has thyroidectomy but they are euthyroid.
DM - diabetes mellitus

Thyroid antibodies were available for 600 (67%) T2DM patients and 282 subjects in control group. Positive TPOab was found in 50 T2DM patients (8.3%) versus 29 (10.3%) in control group p=0.412. Both had a positive thyroid antibodies. Positive both thyroid antibodies TPOab and Tgab were found in 15 T2DM patients (2.5%) versus 17 (6%) in controls p=0.015. Of the 53 T2DM patients with previous disease only 7 had a data on thyroid antibodies with a negative results. Of the 60 T2DM patients who were found to have thyroid dysfunction, 14 were positive for TPOab and Tgab, 4 with overt hypothyroidism and 10 with subclinical hypothyroidism, while of 20 subjects, who were found to have thyroid dysfunction in control subjects, 5 had positive Tab, 4 had subclinical hypothyroidism and one had an overt hypothyroidism. No hyperthyroid cases were found in both groups with positive Tab.

Discussion. The prevalence of thyroid dysfunction represented by hyperthyroidism, hypothyroidism and subclinical hypothyroidism and hyperthyroidism was examined in adult population in the Whickham survey and was reported to be 6.6%.[1] The incidence of thyroid disorders was increasing during the follow up of the same population.[10] The association between DM and thyroid disease has been recognized, though the reported prevalence of thyroid dysfunction in diabetic populations varies widely between studies.[5,6,11,12] This association may support the view that diabetic patients should be screened for thyroid dysfunction annually.

At the time of screening, none of the patients and controls including the newly discovered cases had symptoms indicative to thyroid disease. In the present study, the prevalence of elevated TSH in the newly diagnosed thyroid dysfunction was 33 (6.9%) female and 15 (3.5%) T2DM patients, where in the control group the prevalence of elevated TSH was 11 (6.4%) female subjects and 7 (5.4%) male subjects. These results are comparable with previously reported results.[1],[5,6,11] As the subclinical hypothyroidism with positive Tab almost inevitably progresses to overt hypothyroidism[13,14] the use of thyroxine replacement was justified.

Subclinical hyperthyroidism is a heterogeneous clinical entity, and may have important effects on the heart and bony skeleton.[15,16,20] The prevalence of hyperthyroidism, including subclinical in the newly discovered cases was 2.1% in female (10 patients) and 0.4% in male (2 patients) T2DM patients; and in the control group was 1.2% in female (2 patients) and absent in male subjects. The prevalence of hyperthyroidism was much lower than hypothyroidism but higher than in the control group and higher than the prevalence reported in the general population (0.3% for females and less than 0.1% for males).[1] The present study showed an overall prevalence of thyroid dysfunction of 12.5% in T2DM patients. The prevalence of overt and subclinical hypothyroidism was 10.3%, (14.2% in females and 5.8% in males) and the overall prevalence of hyperthyroidism, including subclinical hyperthyroidism was 1.7% (2.3% in females and 0.9% in males) (**Table 2**). The overall prevalence of thyroid dysfunction in the control group was 6.6%. The prevalence of overt and subclinical hypothyroidism in the control group was 6% (7.4% in females and 5.4% in males) and the prevalence of hyperthyroidism including subclinical was 0.6% (1.2% in females and absent in males). There was a significant difference in the prevalence of thyroid dysfunction between T2DM patients (12.5%) and the controls (6.6%) p=0.0064

In T2DM patients, the association of thyroid disease is unexplained. It may be related to the older age of the type T2DM patients; as elderly people are having an increased risk of thyroid disease.[4] It may also be related to the fact that some T2DM patients actually have type 1 diabetes mellitus with a very slow onset and hence, they have the same genetic predisposition toward autoimmune disease as patients with type 1 diabetes.[17,18] The benefits of identifying thyroid dysfunction at an early stage, and even in a symptomatic patient are considerable because progression to overt thyroid dysfunction is associated with consequent morbidity including the adverse effects on lipid[19] and bone metabolism.[16]

In conclusion, this study has demonstrated a high prevalence of thyroid disease in diabetic patients in comparison with the control group. Screening for thyroid disease in diabetic patients may be justified for early detection and treatment of thyroid dysfunction in diabetic patients in whom thyroid symptoms, if present, may be masked by diabetic state.

Acknowledgment. This study was supported by the Higher Council of Science and Technology and Jordan University, Jordan. Authors would like to thank Ms. Rania Kakish for the secretarial assistance and Mr. Mustafa Radaideh for helping with the statistical analysis. Special thanks for Lama Jamhawi who assisted the final preparation of the manuscript.

References

1. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F. The spectrum of thyroid disease in a community: the Whickham survey. ***Clin Endocrinol (Oxf)*** 1977; 7: 481-493.
2. Kallner A, Kallner G, Lundell G, Sjoberg HE. Highly sensitive assays of serum thyrotropin in the diagnosis of hypothyroidism: assessment of performance and reference values. ***Scand J Clin Lab Invest*** 1987; 47: 157-164.
3. Fisher DA. Effectiveness of newborn screening programs for congenital hypothyroidism: prevalence of missed cases. ***Pediatr Clin North Am*** 1987; 34: 881-890.

4. Rae P, Farrar J, Beckett G, Toft A. Assessment of thyroid status in elderly people. ***BMJ*** 1993; 307: 177-180.
5. Feely J, Isles TE. Screening for thyroid dysfunction in diabetics. ***Br Med J*** 1979; 1: 1678.
6. Gray RS, Borsey DQ, Seth J, Herd R, Brown NS, Clarke BF. Prevalence of subclinical thyroid failure in insulin dependent diabetes. ***J Clin Endocrinol Metab*** 1980; 50: 1034-1037.
7. Ajlouni K, Jaddou H, Batieha A. Diabetes and impaired glucose tolerance in Jordan: prevalence and associated risk factors. ***J Intern Med*** 1998; 244: 317-323.
8. Radiadeh A, Khateeb M, Bateiha A, Nasser A, Ajlouni K. Thyroid function and thyroid autoimmunity in patients with type 1 diabetes mellitus. ***Saudi Med J*** 2003; 24: 352-355.
9. Landenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy E et al. American thyroid association guidelines for detection of thyroid dysfunction. ***Arch Intern Med*** 2000; 160: 1573-1575.
10. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty year follow up of whickham survey. ***J Clin Endocrinol*** 1995; 43: 55-68.
11. Gray RS, Borsey DQ, Seth J, Herd R, Brown NS, Clarke BF. Unrecognized thyroid failure in diabetes mellitus. ***J Clin Lab Immunol*** 1979; 2: 221.
12. Perros P, McCrimmon RJ, Shaw G, Frier BM. Frequency of thyroid dysfunction in diabetic patients, value of annual screening. ***Diabet Med*** 1995; 12: 622-627.
13. Evered D, Hall R. Hypothyroidism. ***Br Med J*** 1972; 1: 290-295.
14. Tunbridge WM, Brewis M, French JM, Appleton D, Bird T, Clark F et al. Natural history of anti-immune thyroiditis. ***Br Med J (Clin Res Ed)*** 1981; 282: 258-262.
15. Leslie PJ, Toft AD. The replacement therapy problem in hypothyroidism. ***Bailliere's Clin Endocrinol Metab*** 1988; 2: 653-669.
16. Foldes J, Tarjan G, Szathmari M, Varga F, Krasznai I, Horvath C. Bone mineral density in patients with endogenous subclinical hyperthyroidism: is this thyroid status a risk factor for osteoporosis? ***Clin Endocrinol (Oxf)*** 1993; 39: 521-527.
17. Riley WJ, Maclaren NK, Lezzotte DC, Spillar RP, Rosen Bloom AL. Thyroid autoimmunity in insulin dependent diabetes mellitus the case for routine screening. ***J Pediatr*** 1981; 99: 350-354.
18. Kontiancn S, Schlenzka A, Koskimes S, Rilva A, Maenpaa J. Autoantibodies and autoimmune diseases in young diabetics. ***Diabetes Res*** 1990; 13: 151-156.
19. Althans BU, Staub JJ, Ryff-de Leche A, Oberhansli A, Stahelin HB. LDL/HDL–changes in subclinical hypothyroidism; possible risk factors for coronary heart disease. ***Clin Endocrinol*** 1988; 28: 157-163.
20. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low serum thyrotropin concentrations as risk factor for atrial fibrillation in older persons. ***N Engl J Med*** 1994; 331: 1249-1252.