Autoimmune thyroid disease in children and adolescents with type 1 diabetes mellitus in Northwest Iran

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ABSTRACT

الأهداف: التحقيق في انتشار مرض الدرقية ذاتي المناعة لدى الأطفال المصابين بداء السكري.

الطريقة: أجريت دراسة على شريحة عرضية شملت خلال في الفترة ما بين فبراير 2006م وحتى نوفمبر 2007م، شملت الأطفال الذين تم تحويلهم إلى عيادة الغدد الصماء للأطفال بجامعة تبريز للعلوم الطبية – تبريز – إيران. تم قياس مستويات مصل مضادات البيروكسيد، الأجسام المضادة لمضادات التيروغلوبلين، هرمون الثيروتروبين بواسطة طريقة اليسا لـ176 طفلاً مصابا بداء السكري (78 ذكر– 98 أنثى)، وبلغ متوسط العمر 8.3±3.7، وفترة داء السكري الرئيسية 1.6±2.5 سنوات.

النتائج: تبين وجود مرض الدرقية ذاتي المناعة لدى 12% من المرضى (8.6% إناث، 3.4% ذكور) تبين وجود المستويات الملحوظة لدى مضادات البيروكسيد (10.2%). مضادات التيروغلوبلين (8%) وكلا الأجسام المضادة (6.3%) في جميع المرضى.

خاتمة: مرض الدرقية ذاتي المناعة لدى الأطفال والمراهقين الإيرانيين المصابين بداء السكري من النوع الأول لديه معدل انتشار متوسط مقارنة مع أولئك في الدول الأخرى. هذا المرض أكثر شيوعاً لدى الإناث ومرضى السكري كبار السن.

Objectives: To investigate the prevalence of autoimmune thyroid disease in diabetic children in Northwest Iran.

Methods: In a cross-sectional study from February 2006 to November 2007, serum levels of anti-thyroid peroxidase, and anti-thyroglobulin antibodies, and thyrotropin hormone were measured with ELISA method in 176 diabetic children (78 Male and 98 Female) at a mean age of 8.3±3.7 and mean diabetes duration of 1.6±2.5 years, who were referred to the Pediatric-Endocrinology Clinic of Tabriz University of Medical Sciences, Tabriz, Iran.

Results: Autoimmune thyroid disease was found in 12% of patients (8.6% female, and 3.4% male). Significant levels were found for anti-thyroid peroxidase (10.2%), anti-thyroglobulin (8%), and both antibodies (6.3%) in all patients.

Conclusion: We concluded that autoimmune thyroid disease in Iranian children, and adolescents with type 1 diabetes has a medium prevalence rate compared with those of other countries. The disease is more common in female, and older diabetic patients.

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It has been known for more than 30 years that Type-1 Diabetes Mellitus (T1DM), is a chronic autoimmune disease characterized by self-destruction of the pancreatic beta-cells, and the presence of autoantibodies directed against beta-cells' components, and endogenous insulin.[1,2] Type-1 Diabetes Mellitus as a common autoimmune endocrine disease of children and adolescents is frequently associated with the other autoimmune disorders and autoantibodies.[3] Autoimmune thyroid disease (ATD) that can be recognized by high anti-thyroid peroxidase (a-TPO) and/or anti-thyroglobulin (a-Tg) titers is the most prevalent autoimmune disease associated with T1DM.[4,5] Some studies have shown that thyroid dysfunction may disturb metabolic control in T1DM, causing a more severe diabetes when it is accompanied by ATD,[6] however, this impact has not been corroborated by other studies.[7] The prevalence of ATD in diabetic patients considerably varies in different countries depending on age, gender, and ethnic origin

of the subjects.[8-13] Despite the abundance of studies concerning the same matter world-wide, there are still debates on the situation in the Iranian population, especially in children. The aim of this study was to investigate the presence of ATD among diabetic children and adolescents in Northwest Iran, as our clinic is the only referral center for pediatric endocrinology in this area.

Methods. This cross-sectional study was carried out from February 2006 to November 2007. All children and adolescents with T1DM presenting to the outpatient Pediatric-Endocrinology Clinic of Tabriz University of Medical Sciences (the only University-affiliated clinic for Pediatric-Endocrinology in Northwest Iran), were included. Patients older than 18 years of age and ones who refused to be tested for presence of anti-thyroid autoantibodies were excluded. One hundred and seventy-six children and adolescents with T1DM were enrolled in the study. (The study protocol was approved by Ethic Committee and Research Vice Chancellor Office of Tabriz University of Medical Sciences).

Laboratory tests. Written informed consent was taken and blood samples were collected to assay the a-TPO, a-Tg and serum thyrotropin (TSH) levels. The UK-made Diagnostics® thyroglobulin IgG ELISA kit (GENESIS, Cambridge, UK), product code GD48 was used for evaluation of serum levels of a-Tg, and thyroid-peroxidase IgG ELISA kit, product code GD49, was used for evaluation of serum levels of a-TPO antibodies. Values above 75 U/ml for a-TPO and above 100 IU/ml for a-Tg have been considered positive and either one or both positive antibody level(s) diagnostic for ATD. The USA-made AccuBindTM ELISA Microwells kit (MONOBIND, Costa Mesa, USA), product code 325-300, was used for measurement of serum TSH level. The normal TSH level as determined by the instruction of this kit is 0.4-6.21 micIU/ml.

Statistical analysis. We used chi-square test, t-test, and Pearson's correlation by employing SPSS software version 14 for statistical analysis. Quantitative variables are presented as mean±SD, and qualitative variables as percent; $p<0.05$ has been considered significant.

Results. One hundred and seventy-six children, including 78 males (44.3%) and 98 females (55.7%) with T1DM at the mean age of 8.3±3.7 years (range: 1-18 years) and mean diabetes duration of 1.6±2.5 years were evaluated. There was no significant difference between males and females regarding their age (7.7±3.8 versus 8.8±3.6 years, $p=0.052$), and duration of diabetes (1.5±1.7 versus 1.7±2.9 years, $p=0.554$). **Table 1** shows the frequency of seropositive state for ATD, comparing male and female patients with T1DM. Among antibody-positive children, girls were 8.75 times more likely to be seropositive for both antibodies than boys (95% Confidence Interval 1.09-69.91). In

Table 1 - The frequency of seropositive state for autoimmune thyroid disease, comparing male and female patients with type 1 diabetes mellitus (N=176).

Positive antibody	Total n (%)	Male n (%)	Female n (%)	*P*-value
Anti-TPO	18 (10.2)	5 (2.8)	13 (7.4)	0.136
Anti-Tg	14 (8)	2 (1.1)	12 (6.9)	0.017
Both Antibodies	11 (6.3)	1 (0.6)	10 (5.7)	0.015
Either one or both antibodies	**21 (12)**	**6 (3.4)**	**15 (8.6)**	0.116

TPO - Thyroid peroxidase, Tg - Thyroglobulin

Table 2 - Age distribution of the patients and frequency of seropositive state for autoimmune thyroid disease, in different age groups.

Age groups (Year)	All patients n (%)	a-thyroid peroxidase n (%)	a-thyroglobulin n (%)	Both antibodies n (%)	Either one or both antibodies n (%)
<5	35 (19.9)	3 (1.7)	2 (1.1)	2 (1.1)	3 (1.7)
5-10	82 (46.6)	5 (2.8)	5 (2.8)	3 (1.7)	7 (4)
>10	59 (33.5)	10 (5.7)	7 (4)	6 (3.4)	11 (6.3)
Total	**176 (100)**	**18 (10.2)**	**14 (8)**	**11 (6.3)**	**21 (12)**

Table 2, age distribution of the patients and frequency of seropositive state for ATD, in different age groups were shown. In patients with ATD (seropositive for at least one antibody, N=21) the mean serum TSH levels were 4.3±3.8 and in patients without ATD (seronegative for both antibodies, N=155), the mean serum TSH levels were 2.9±2 micIU/ml, (p=0.103); indicating that TSH level is not significantly higher in T1DM patients who are seropositive for ATD compared with seronegative ones. Three females (27.3%) of 11 patients (1 male and 10 female patients) had positive levels for both a-TPO, and a-Tg, they showed serum TSH levels higher than 10 micIU/ml without clinically obvious goiter on physical examination (ultrasound was not performed). No patient received thyroid therapy during this study. There was no significant difference (p=0.422) between mean serum THS levels of seropositive patients for both antibodies (4.1±3.5) and those seropositive for only one antibody (3.1±1.4). There was a positive linear correlation between serum TSH level and duration of diabetes in seropositive subjects for one (r=0.505, p=0.023) or both (r=0.790, p=0.007) antibodies that are markers of ATD; however, we did not find such a correlation in seronegative subjects (r=0.131, p=0.127). The frequency of presentation with ketoacidosis (DKA) at the onset of diabetes showed no statistically meaningful difference between seropositive (42.9%) and seronegative (37.4%) patients (p=0.630).

Discussion. The results of this study show that the prevalence of ATD, as diagnosed by positive serum levels of a-TPO and/or a-Tg, is 12%, and a-TPO is more prevalent than a-Tg in our children, and adolescents with T1DM. In addition, the disease is more prevalent in females, and older patients. These findings are compatible with several reports from different countries. The prevalence of ATD varies world-wide depending on the age, gender, and ethnic background of the studied subjects.[4] Its prevalence in children with T1DM varies considerably, ranging from 3-54.3% in different countries.[14,15] The lowest prevalence rate (3%) has been found in American children[14] and the highest one (54.3%) reported from India.[15] In a multi-center study (Italy, Austria, Croatia, and Slovenia) Radetti et al[14] found a prevalence rate of 3.9% in 1419 children with T1DM, and recommended that children with T1DM should be screened for thyroid autoantibodies, and those who are positive should undergo periodic thyroid function tests. In a report from Belgium, positive a-TPO levels were found in 16.1% of 286 diabetic children, and in 24.7% of 497 diabetic adults, with a female preponderance.[16] Another study on Indian diabetic children showed 54.3% of them to be seropositive for a-TPO, and 31.4% of them to be seropositive for a-Tg antibodies. However, contrary to our study, the prevalence of antibodies was not different between boys, and girls in this Indian study.[15] In a report from Brazil on 474 diabetic patients (9 months to 25 years old), 16.7% of them, predominantly girls, had positive levels of anti-thyroid antibodies.[17] A study on German diabetic children revealed high serum levels of a-TPO and a-Tg in 15.4% and 14.4% of cases, respectively. In this study, elevated serum levels of a-TPO and a-Tg antibodies were detected more often in girls than in boys.[18] According to our data, diabetic children with significantly raised levels of both a-TPO, and a-Tg are more prone to sustain hypothyroidism, and girls are affected more frequently than boys; this resembles the majority of other studies indicating that ATD, and hypothyroidism are more common in diabetic females than males,[8,16-21] but a few studies have failed to demonstrate such a female gender preponderance in thyroid abnormalities complicating diabetic patients.[15,22,23] We did not find any difference in the prevalence rate of ATD between children presented with DKA, and those without. However, a study on adult patients with recently diagnosed T1DM, by Lacasa et al,[24] showed that patients with thyroid-autoimmunity had lower bicarbonate levels, and more severe forms of clinical presentation. They suggested that prospective studies are required to determine the long-term relevance of this finding.

There was a limitation in our study regarding the sample size; although our center is the only university-affiliated clinic for pediatric endocrinology in the Northwest of Iran, however, we could not cover so many cases of T1DM since our research ethical policy necessitates the enrollment of only those patients who voluntarily given their written consent.

We concluded that associated ATD in T1DM has a medium prevalence rate in our children and adolescents compared with other countries. This situation is more common in females and older T1DM patients. Subjects who are concomitantly seropositive for both a-TPO and a-Tg have a significant susceptibility to sustain thyroid dysfunction. It is seriously recommended to measure a-TPO and a-Tg serum levels in type-1 diabetic children and adolescents periodically; and then serum TSH level in those proved seropositive, especially for both markers; however, there is no generally accepted protocol for such a screening.

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References

1. Bottazzo GF, florin-Christensen A, Doniach D. Islet cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. ***Lancet*** 1974; 2: 1279-1283.
2. Eisenbarth GS. Type diabetes mellitus a chronic autoimmune disease. ***N Engl J Med*** 1986; 314: 1360-1368.
3. Araujo J, Brandao LA, Guimaraes RL, Santos S, Falcao EA, Milanese M, et al. Prevalence of autoimmune thyroid disease and thyroid dysfunction in young Brazillian patients with type 1 diabetes. ***Pediatr diabetes*** 2008; 9: 272-276.
4. Hanukoglu A, Mizrachi A, Dalal I, Admini O, Rakover Y, Bistritzer Z, et al. Extrapancreatic autoimmune manifestation in type 1 diabetes patients and their first-degree relatives. ***Diabetes Care*** 2003; 26: 1235-1240.
5. Prazny M, Skrha J, Limanova Z, Vanickova Z, Hilgertova J, Prazna J, et al. Screening for associated autoimmunity in type 1 diabetes mellitus with respect to diabetes control. ***Physiol Res*** 2005; 54: 41-48.
6. Franzese A, Buono P, Mascolo M, Leo AL, Valerio G. Thyroid autoimmunity starting during the course of type 1 diabetes denotes a subgroup of children with more severe diabetes. ***Diabetes Care*** 2000; 23; 1201-1202.
7. Fernandez-Castaner M, Molina A, Lopez-Jumenez L, Gomez JM, Soler J. Clinical presentation and early course of type 1 diabetes in patients with and without thyroid autoimmunity. ***Diabetes Care*** 1999; 22: 377-381.
8. Kordonouri O, Klinghammer A, Lang EB, Grusters-Kieslich A, Grabert M, Holl RW, et al. Thyroid autoimmunity in children and adolescents with type 1 diabetes. ***Diabetes Care*** 2002; 25: 1346-1350.
9 Szypowska A, Blazik M, Groele L, Pankowska E. The prevalence of autoimmune thyroid disease and celiac disease in children and adolescents with type 1 diabetes mellitus. ***Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw*** 2008; 14: 221-224.
10. Rattarasarn C, Diosdado MA, Ortego J, Leelawattana R, Soonthornpun S, Setasuban W, et al. thyroid autoantibodies in Thai type 1 diabetic patients: clinical significance and their relationship with glutamic acid decarboxylase antibodies. ***Diabetes Res Clin Pract*** 2000; 49: 107-11.
11. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, Gruters-Kieslich A. Predictivity of thyroid autoantibodies for the development of thyroid disorder in children and adolescents with type 1 diabetes. ***Diabet Med*** 2002; 19: 518-521.
12. Czerniawska E, Szalecki M, Piatkowska E, Mlynarski W, Bodalski J, Lewinski A. Prevalence of thyroid antibodies (TPO and ATG) at the onset of type 1 diabetes mellitus in children treated in two diabetic centers in Lodz and Kielce. ***Med Wieku Rozwoj*** 2003; 7: 223-228.
13. Rakosnikova V, Zahradnikova M, zikmund J, Pruhova S, Lebi J. Normal course of autoimmune thyroid disease in diabetic children. ***Cas Lek Cesk*** 2003; 142: 235-239.
14. Radetti G, Paganini C, Gentili L, Bernasconi S, Betterle C, Borkenstein M, et al. Frequency of hashimoto's thyroiditis in children with type 1 diabetes mellitus. ***Acta Diabetol*** 1995; 32: 121-124.
15. Menon PS, Vaidyanathan B, Kaur M. Autoimmune thyroid disease in Indian children with type 1 diabetes mellitus. ***J Pediatr Endocrinol Metab*** 2001; 14: 279-286.
16. De Leeuw IH, De Block CEM. Is type 1 diabetes often associated with other autoimmune disease? A cross-sectional study in Belgium. ***Proc R Coll Physicians Edinb*** 2001; 31: 112-117.
17. Mantovani RM, Mantovani LM, Dias VM. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: prevalence and risk factors. ***J Pediatr Endocrinol Metab*** 2007; 20: 669-675.
18. Kordonouri O, Hartmann R, Deiss D, Wilms M, Gruters-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.
19. De Block CE. Diabetes mellitus type 1 and associated organ-specific autoimmunity. ***Verh K Acad Geneeskd Belg*** 2000; 62: 285-328.
20. Umpierrez GE, Latif KA, Murphy AE, Lambeth HC, Stentz F, Bush A, et al. thyroid dysfunction in patients with type 1 diabetes: longitudinal study. ***Diabetes Care*** 2003; 26: 1181-1185.
21. Gonzalez GC, Capel I, Rodriguez-Espinosa J, Mauricio D, De Leiva A, Perez A. thyroid autoimmunity at onset of type 1 diabetes as predictor of thyroid dysfunction. ***Diabetes Care*** 2007; 30: 1611-1612.
22. Kalicka-Kasperczyk A, Dziatkowak H, Bartnik-Mikuta A, Pituch-Noworolska A, Kasperczyk K, Nazim J, et al. Thyroid peroxidase antibodies and thyroid disease in children and adolescents with newly diagnosed type I diabetes. ***Przegl Lek*** 2002; 59: 509-513.
23. Maugendre D, Guilhem I, Karacatsanis C, Poirier JY, Leguerrier AM, Lorcy Y, et al. Anti-TPO antibodies and screening of thyroid dysfunction in type 1 diabetes patients. ***Ann Endocrinol (Paris)*** 2000; 61: 524-530.
24. Molina Lacasa A, Fernandez Castaner M, Perez Maraver M, Lopez Jimenez L, Gomez Saez JM, Soler Ramon J. Autoimmune thyroid pathology in recently diagnosed diabetes mellitus type 1. ***Rev Clin Esp*** 1998; 198: 818-821.

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Mofid AR, Yazdani T, Shahrzad M, Seyedalinaghi S, Zandieh S. Role of fine-needle aspiration in the management of thyroid nodules. ***Saudi Med J*** 2009; 30: 515-518.

Sadat-Ali M, Alelq AH. Effect of androgens on bone mineral density in Saudi Arabian males above the age of 50 years. ***Saudi Med J*** 2007; 28: 1247-1250.

Soliman KB, Abbas MM, Seksaka MA, Wafa S, Balah AS. Aggressive primary thyroid non Hodgkin's lymphoma with pregnancy. ***Saudi Med J*** 2007; 28: 634-636.