MÆDICA - a Journal of Clinical Medicine

STATE OF THE ART

MAEDICA – a Journal of Clinical Medicine
2016; 11(4):308-312

Type 1 Diabetes and Thyroid Autoimmunity in Children

Anca ORZAN[a,b], Carmen NOVAC[a,b], Mihaiela MIHU[a], Constantin IONESCU TIRGOVISTE[b,c], Mihaela BALGRADEAN[a,b]

[a] „Marie Curie" Emergency Children's Hospital, Bucharest, Romania

[b]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[c]"Prof Dr N Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest

ABSTRACT

Introduction: *Autoimmune thyroid disease and type 1 diabetes (T1DM) are two autoimmune diseases frequently associated, especially in pediatric population.*

Aims: *we wanted to determine and ilustrate the relationship between type 1 diabetes and autoimmune thyroiditis and also the factors than can influence it, like gender, age, diabetes duration. Glycemic control was also evaluated for all the patients.*

Materials and methods: *There were studied 256 patients, children and adolescents with T1DM (male/female: 145/115; 55%/45%). Anti-TPO antibodies were detected using the electrohemiluminescence method and glycosylated haemoglobin A1c (HbA1c) was measured through a imunoturbidimetric method. The patients were clinically examined, including thyroid gland palpation, blood pressure measurement and assessment of their pubertal status and growth.*

Results: *Age distribution at the time of T1DM diagnosis: most of them, 26% were diagnosed between 6 and 9 years, 23% between 1-3 years, 21% between 3-6 years, 19% between 9-12 years, 9% between 12-15 years, and very few of them (2%) were diagnosed between 15 and 18 years. Among these patients, 47/256 (18.3 %) were positive for thyroid antibodies (anti - TPO). In 2 of 47 patients tests for anti TPO antibodies were positive at the time of T1DM diagnosis. Tests for anti – TPO antibodies became positive with an average of 5.09±3.84 (range 0-13) years after the diagnosis of T1DM. At the time that anti – thyroid antibodies were first seen to be positive all patients were euthyroid with a mean age of 11.3 years (range 4 -16) and a mean diabetes duration of 5.21±3.57 (range 0-9 years). After 5±3.3 years (range 0- 9 years) a progression towards subclinical hypothyroidism due to Hashimoto thyroiditis was observed in 41 from 47 patients (87.2%), while no patient developed clinical hypoythyroidism.*

It was observed an 9.2 % ±1.5% mean value of HbA1c in patients with thyroiditis comparative with 7.9 % ± 0.7 % mean HbA1c value in those without thyroiditis.

Conclusions: *Thyroid autoimmunity is frequently present among T1DM patients, can be associated with increased age, female gender, long diabetes duration, and can inbalance the glycemic control of T1DM patients.*

Keywords: Children, type 1 diabetes, autoimmune thyroiditis, thyroid autoantibodies

Address for correspondence:
Anca Andreea Orzan
Postal Address: 20th Constantin Brancoveanu Boulevard, 4th District, Bucharest, Romania.
Phone number : 0729805497
E-mail: anca.orzan@gmail.com

Article received on the 10rd of October 2016. Article accepted on the 09rd of January 2017.

INTRODUCTION

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications (1).

Type 1 diabetes accounts 5–10% of diabetes and is due to cellular-mediated autoimmune destruction of the pancreatic b-cells but three-quarters of all cases of type 1 diabetes are diagnosed in individuals < 18 years of age. It is defined by one or more autoimmune markers, including islet cell autoantibodies and autoantibodies to insulin, GAD (GAD65), the tyrosine phosphatases IA-2 and IA-2b, and ZnT8. The disease has strong HLA associations, with linkage to the DQA and DQB genes. These HLA-DR/DQ alleles can be either predisposing or protective (2). The rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are not typically obese when they present with type 1 diabetes, obesity should not preclude the diagnosis (3). These patients are also prone to other autoimmune disorders such as Hashimoto thyroiditis, celiac disease, Graves disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (2).

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with type 1 diabetes (4). At the time of diagnosis, about 25% of children with type 1 diabetes have thyroid autoantibodies (5). Their presence is predictive of thyroid dysfunction and most commonly hypothyroidism, although hyperthyroidism occurs in 0.5% of cases (6). Thyroid function tests may be misleading (euthyroid sick syndrome) if performed at time of diagnosis owing to the effect of previous hyperglycemia, ketosis or ketoacidosis, weight loss, etc. Therefore, thyroid function tests should be performed soon after a period of metabolic stability and good glycemic control. Subclinical hypothyroidism may be associated with increased risk of symptomatic hypoglycemia (7) and reduced linear growth rate. Hyperthyroidism alters glucose metabolism and usually causes deterioration of metabolic control.

Different factors have been associated with the development of thyroid autoimmunity in the general population, such as heredity, increasing age, female gender, puberty, oestrogen use, pregnancy and an iodine-rich diet (8-10). In adults with T1DM, female gender, increasing age, and the presence of glutamic acid decarboxylase antibodies (anti-GAD) have been associated with the development of thyroid autoimmunity (11). Also in children and adolescents with T1DM, previous studies agree on the age and gender effect (12-16), while there are very limited studies on the significance of the persistence of anti-GAD (11), the age at diabetes diagnosis (12,14), and diabetes duration (14,16,17) on the development of thyroid antibody positivity.

The aims of this study were to identify in Romanian children and adolescents admitted in the "MS Curie" Emergency Children's Hospital from Bucharest, the prevalence of thyroid antibody positivity and to determine the effect of potential risk factors, such as current age, age at onset of diabetes, duration of diabetes on its development and also the influence on glycemic control of autoimmune thyroiditis. ❑

MATERIAL AND METHODS

The study population included 256 children and adolescents (male/female: 145/115; 55%/45%) with T1DM, follwed – up in "MS Curie" Emergency Children's Hospital – Diabetes Department, diagnosed in the period of 1st of January 2001 – 1st of July 2016. Informed consent was obtained from each parent before blood sampling.

The criteria for the diagnosis of T1DM were : fasting plasma glucose levels of 126 mg/dl or symptoms of hyperglycaemia (polyuria, polydipsia, and unexplained weight loss with a random plasma glucose ≥200 mg/dL , or 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test. Apart from marked hyperglycaemia, the diagnosis of T1DM is usually associated with the presence of diabetic ketoacidocis (DKA). Among our patients, 58% presented with DKA

(pH < 7.30) and 42% without (pH ≥ 7.30). From the patients with DKA 56% were males and 44% were females.

Every three or six months, during hospital visit, the patients were clinically examined, including thyroid gland palpation, blood pressure measurement, and assessment of their pubertal status and growth.

To see the age distributions at the time of T1DM diagnosis the patients were clasified in age groups. It was observed that most of them were diagnosed between 6 and 9 years (26%), the second peak of incidence was seen at 1 -3 years (23%), followed by 3-6 years (21%), 9-12 years (19%), 12-15 years (9%), 15 -18 years (2%).

Anti-TPO antibodies were detected using the electrohemiluminescence method (ECLIA) from venous blood sampling. The upper normal limit for the anti-TPO antibodies was set at 34 UI/mL. Values greater than these cut-off values were considered as positive. For the evaluation of thyroid function FT4 (free-thyroxine) levels were measured using the same electrochemiluminescence method (ECLIA). Thyroid ultrasonography was performed in all patients with elevated titres of anti-thyroid antibodies, combined with thyroid enlargement and/or elevated TSH levels. The presence of thyroid enlargement (thyroid gland volume > 97th age-related percentile) with diffuse hypoechogenicity and/or diffuse micronodules confirmed the diagnosis of autoimmune thyroiditis.The diagnosis of subclinical autoimmune thyroiditis (SAIT) (Hashimoto's) was based on high levels of TSH (>5 μIU/mL), associated with the presence of at least one thyroid autoantibody on two or more consecutive occasions, and/or with ultrasonographic findings of thyroiditis. Clinical hypothyroidism was associated, in addition to the above, with low FT4 levels and/or the presence of goitre. In all cases of hypothyroidism (subclinical or clinical) with positive anti-thyroid antibodies, with/without goitre, L-thyroxine administration was started.

Glycosylated haemoglobin A1c (HbA1c) was measured through a imunoturbidimetric method (DCCT standardized: Diabetes Control and Complications Trial and NGSP certificated: National Glycohemoglobin Standardization Program). The normal range was 4.8%–6.4%.

This study has been statistically evaluated, using Microsoft Excel and IBM SPSS Statistics 23 for Windows. In cases in which the p value was assessed, results <0.05 were considered significant. The p value was assessed through the Anova test, the Mann-Whitney U test and the Wilcoxon test. ❑

RESULTS

The study is based on 256 children and adolescents (male/female: 145/115; 55%/45%) diagnosed with T1DM. Age distribution at the time of T1DM diagnosis: most of them, 26% were diagnosed between 6 and 9 years, 23% between 1 -3 years, 21% between 3-6 years , 19% between 9-12 years, 9% between 12-15 years, and very few of them (2%) were diagnosed between 15 -18 years.

Majority of the individuals (58%) presented with diabetic ketoacidosis at onset of T1DM, with a higher tendency of males for developing ketoacidosis (56%).

Among our patients, 47/256 (18.3 %) were positive for thyroid antibodies (anti - TPO). In 2 of 47 patients tests for anti TPO antibodies were positive at the time of T1DM diagnosis. Tests for anti – TPO antibodies became positive an average of 5.09 ±3.84 (range 0-13) years after the diagnosis of T1DM.

At the time that anti – thyroid antibodies were first seen to be positive all patients were euthyroid with a mean age of 11.3 years (range 4 -16) and a mean diabetes duration of 5.21±3.57 (range 0-9 years). After 5 ± 3.3 years (range 0- 9 years) a progression towards subclinical hypothyroidism due to Hashimoto thyroiditis was observed in 41 from 47 patients (87.2%), while no patient developed clinical hypoythyroidism. This diagnosis was based on the presence of elevated serum TSH concentrations (> 5 μIU/ml) and normal fT4 values, associated with a positive test for anti –TPO antibody and/or with ultrasonographic findings of thyroiditis. After the diagnosis of subclinical hypothyroidism, they received treatmenr with L – thyroxine at a dose between 25-100 μg. Out of those 47 patients, 2 of them developed hiperthyroidism and were treated with Thiamazole (Thyrozol) at a dose of 5-10 mg/daily.

It was not observed any significant effect of anti-thyroid antibody positivity on the growth and BMI status of the children with diabetes.

After identifying the patients with expressed thyroid autoimmunity we wanted to see if this

			Sum of Squares	df	Mean Square	F	Sig.
Mean HbA1c value after developing thyroiditis * Thyroiditis positive Dx	Between Groups	(Combined)	13.947	1	13.947	5.984	0.015
	Within Groups		561.72	241	2.331		
	Total		575.666	242	16.278		

TABLE 1. (Anova table). Significance of the p value of 0.015, which reflects the difference between glycemic control in T1DM patients with thyroiditis and those without.

influenced the glycemic control of these patients. It was observed an 9.2 % ±1.5% mean value of HbA1c in patients with thyroiditis comparative with 7.9 % ±0.7 % mean HbA1c value in those without thyroiditis (p value 0.015 – see tabel 1). ❑

DISCUSSION

This present study was made to ilustrate the prevalence of thyroid antibody positivity and of autoimmune thyroiditis in children and adolescents with T1DM from a Romanian lot of patients. We focused our attention on the effect of age at diabetes diagnosis and diabetes duration on the development of thyroid autoimmunity. The study is based on a long term follow–up of the patients to follow the progres from thyroid antibody positivity to hypothyroidism (subclinical/clinical) or hyperthyroidism, and also the effect of a second autoimmune disease association to diabetes on the children glycemic control and of course on the children´s growth.

The prevalence rate of antithyroid antibodies in the T1DM patients of our study was 18.3%, while a very significant percentage (87.2 %) of them presented subclinical autoimmune hypothyroidism in time and 4.2 % developed hyperthyroidism. Our results are in agreement with previous studies in this age group, reporting a prevalence of 16 – 18.7% (18-20). The prevalence rates of thyroid antibodies postivity in adult T1DM patients are higher than the ones in children reaching a proportion of 29 % while the prevalence of autoimmune thyroiditis in the general population fuctuates from 2-4% and 4-20% (21). Regarding gender distribution it was noticed a significant association of female sex with thyroid antibodies (58.3%), result that is in agreement with other datas from literature (20). Also in general population feminin sex is more prone to develop thhyroid thyroid disease than masculin sex. Actually, sex hormones have been reported to affect the development of antibodies. In patients with T1DM an also in animal model of autoimmune thyroiditis, oestradiol seemed to accelerate the progressin of autoimmuune diseasesvia enhacing the pathway of T helper type 2 (Th2) cells, while androgens had a protecttive effect (19). In this study, the prevalence of thyroid antibodies increased with increasing age and diabetes durations. Our results are corresponding with previous studies (15), reporting that the highest prevalence of thyroid antibodies was observed after the age of 12 years or a diabetes duration of 9 years. This remark can suggest the fact that autoimmune disease is the final phase of a process that starts with autorecognition, passes through immunity with the appearance of autoantibodies and in the end leads to cell distruction and autoimmune disease (22).

Although in their study, Chase at al. (23) reported a reduced rate of growth in children with T1DM and subclinical hypothyroidism that improved under thyroid replacement therapy only in the prepubertal patients, in our study we did not discovered a significant effect of autoimmune thyroiditis on growth and BMI status in T1DM patients.

An important observation of our study was the association of thyroid autoimmunity with the glycemic imbalance. When we comparred HbA1c of T1DM patients with the values from T1DM patients that were associating thyroid autoimmunity we observed higher values of HbA1c for the last ones (9.2 %±1.5%), observation tthat is in agreement with other datas from literature (24). ❑

CONCLUSION

The relationship between thyroid disorders and diabetes mellitus is characterized by a complex interdependent interaction, thyroid autoimmunity being more prevalent in people with

type 1 diabetes. Therefore in T1DM patients is helpful to determine whether anti-TPO antibodies are present. Annual laboratory determinations of anti-TPO antibodies and dosage of TSH should be part of routine tests in the pediatric diabetic population, especially in girls, children with T1DM for more than 5 years, patients above 11 years of age or at those were glicymic control is imbalance without other reasons.

All patients with T1DM should be screened for autoimmune thyroiditis since they are diagnosed with T1DM and every year after that. In case of positive thyroid antibodies there should exist a regular follow up of the thyroid function.❑

Conflict of interests: none declared.
Financial support: none declared.

References

1. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2016;39 (Suppl 1):S1.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014;37(Suppl 1):S81–S90.
3. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2016;39 (Suppl 1):S15.
4. **Roldan MB, Alonso M, Barrio R.** Thyroid autoimmunity in children and adolescents with Type 1 diabetes mellitus. *Diabetes Nutr Metab.* 1999;12:27–31.
5. **Triolo TM, Armstrong TK, McFann K, et al.** Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care* 2011;34:1211–1213.
6. **Dost A, Rohrer TR, Frohlich-Reiterer E, et al.** DPV Initiative and the German Competence Network Diabetes Mellitus. Hyperthyroidism in 276 children and adolescents with type 1 diabetes from Germany and Austria.*Horm Res Paediatr* 2015;84:190–198.
7. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2016;39 (Suppl. 1):S88.
8. **Kaloumenou L, Duntas L, Alevizaki M, et al.** Thyroid volume, prevalence of subclinical hypothyroidism and autoimmunity in children and adolescents. *Journal of the Greek Paediatric Society.* 2007;70:107–14.
9. **Strieder TG, Tijssen JG, Wenzel BE, et al.** Prediction of progression to overt hypothyroidism or hyperthyroidism in female relatives with autoimmune thyroid disease using the Thyroid Events Amsterdam (THEA) score. *Arch Intern Med*. 2008;168:1657–63.
10. **Rose NR, Rasooly L, Saboori AM, Burek CL.** Linking iodine with autoimmune thyroiditis. *Environ Health Perspect.* 1999;107:749–52.
11. **Barova H, Perusicova J, Hill M, et al.** Anti-GAD-positive patients with type 1 diabetes mellitus have higher prevalence of autoimmune thyroiditis than anti-GAD negative patients with type 1 and type 2 diabetes mellitus. *Physiol Res.* 2004;53:279–286.
12. **Kordonouri O, Klinghammer A, Lang EB, et al.** Thyroid autoimmunity in children and adolescents with type 1 diabetes. *Diabetes Care.* 2002;24:1346–50.
13. **Holl RW, Bohm B, Loos U, et al.** Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. *Horm Res.* 1999;52:113–8.
14. **De Block CE, De Leeuw IH, Vertommen JJ, Belgian Diabetes Registry, et al.** Beta-cell, thyroid, gastric, adrenal and coeliac autoimmunity and HLA-DQ types in type 1 diabetes. *Clin Exp Immunol.* 2001;126:236–41.
15. **Mantovani RM, Mantovani LM, Alves Dias VM.** Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: Prevalence and risk factors. *J Pediatr Endocrinol Metab.* 2007;20:669–75.
16. **Barker JM, Yu J, Yu L, et al.** Autoantibody 'subspecificity' in type 1 diabetes. *Diabetes Care.* 2005;28:850–5
17. **Kordonouri O, Hartmann R, Deiss D, et al.** Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty. *Arch Dis Child.* 2005;90:411–4
18. **Karavanaki K1, Kakleas K, Paschali E, et al.** Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (T1DM). *Horm Res.* 2009;71:201-6.
19. **Kakleas K, Paschali E, Kefalas N, et al.** Factors for thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. *Ups J Med Sci.* 2009;114:214–220.
20. **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;20:669-75.
21. **Duntas LH, Orgiazzi J, Brabant G.** The Interface Between Thyroid and Diabetes Mellitus. Clin Endocrinol. 2011;75:1-9.
22. **Talal N.** Autoimmunity and the immunological network. *Arthritis Rheum.* 1978;21:853
23. **Chase HP, Garg SK, Cockerham RS, et al.** Thyroid hormone replacement and growth of children with subclinical hypothyroidism and diabetes. *Diabet Med.* 1990;7:299–303
24. **Hage M, Zantout MS, Azar ST.** Thyroid disorders and diabetes mellitus. *J Thyroid Res.* 2011;2011:439463.