Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 608–611

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Autoimmune thyroiditis in patients with type 1 diabetes mellitus: A long-term follow-up study

Natalia Vallianou*, Theodora Stratigou, Stavroula Koutroumpi, Barbara Vlassopoulou, Stylianos Tsagarakis, George Ioannidis

Department of Endocrinology, Diabetes and Metabolism, Evangelismos Hospital, Athens, Greece

ARTICLE INFO

Article history:
Received 23 October 2018
Accepted 13 November 2018

Keywords:
Type 1 diabetes mellitus
Autoimmune thyroiditis
Anti-Thyroid antibodies
Age
Female sex

ABSTRACT

Aims: In type 1 diabetes mellitus and autoimmune thyroiditis, there seems to be common genetic loci. The purpose of the present study was to determine whether patients with type 1 diabetes had increased prevalence of autoimmune thyroiditis, and which factors were influencing the co-existence of these two clinical entities.

Patients and methods: A cohort of 256 patients, 18–79 years of age, a median duration of diabetes of 20 years and a mean follow-up duration of 13 years were included in the study.

Results: Of the 256 patients with type 1 diabetes, 150 participants (58.6%) were women and 106 (41.4%) were men. One hundred and fifty-nine patients (64.6%) did not have autoimmune thyroiditis, whereas 97 (35.4%) had autoimmune thyroiditis, as was documented by the presence of anti-thyroid antibodies (anti-TPO and/or anti-TG). Of the 97 patients with both diabetes type 1 and autoimmune thyroiditis, 64 (66%) were women and 33 (34%) were men. Among the 97 patients who had both diabetes type 1 and autoimmune thyroiditis, 87 had abnormal levels of both anti-TPO and anti-TG, while 7 patients had subnormal levels of solely anti-TPO and only 3 patients had abnormal levels of only anti-TG.

Conclusions: There was a slightly higher prevalence of autoimmune thyroiditis among our patients with type 1 diabetes mellitus. Also, female sex was predominant, when compared to male sex, among the adult participants of this study. Therefore, regular screening of thyroid function and thyroid autoantibodies may be suggested for all patients with type 1 diabetes.

1. Introduction

As it is widely known, the immune-mediated destruction of pancreatic islet cells causes type 1 diabetes mellitus (DM). Other autoimmune entities, such as Addison disease, Hashimoto thyroiditis, Graves' disease, celiac disease and pernicious anemia are related to type 1 DM [1]. In particular, autoimmune thyroiditis (AIT) is the most common disorder associated with type 1 DM [2]. AIT is characterized by T and B-lymphocyte infiltration of the thyroid gland and the presence of autoantibodies to thyroid peroxidase (anti-TPO) and/or thyroglobulin (anti-TG) [3]. AIT and type 1 DM seem to share a common genetic background. The prevalence of thyroid autoantibodies in children with type 1 DM ranges from 15% to 30% in different countries and populations, a percentage which is significantly higher than that of the general population (1%–4%) [4]. Thyroid autoantibodies can be detected at the initial diagnosis or years after diagnosis of type 1 DM [1,5]. Age of diagnosis and the female gender have been related to the presence of thyroid autoantibodies in children and adolescents with type 1 DM [1,6,7]. In addition, recent studies have reported that the presence of glutamic acid decarboxylase antibodies (GADA) and human leucocyte antigen class II genes may influence the development or progression of AIT [1,5,8]. Therefore, the aim of this study was to evaluate the prevalence of AIT among patients with type 1 DM and identify possible factors, which are associated with this co-existence of both clinical entities.

2. Materials and methods

A cohort of 256 Caucasian patients with DM1, 18–79 years of age, a median of 40 ± 13 years old and a median duration of diabetes of 20 ± 11 years were included in the study. All patients used

* Corresponding author. 5 Pyramidon str., 19005, Municipality of Marathonas, Athens, Greece.
E-mail address: Natalia.vallianou@hotmail.com (N. Vallianou).

https://doi.org/10.1016/j.dsx.2018.11.048
1871-4021/

Table 1
Characteristics of the participants of the study at the beginning and at last follow-up.

	n	AT THE BEGINNING	*n*	AT THE END	p[a]
		MD±SD or *n(%)*		MD±SD or *n(%)*	
Age (years)	256	40 ± 13	–	–	–
Gender					–
Female	–	150 (58.6%)	–	–	
Male	–	106 (41.4%)	–	–	
Smoking					–
No	–	161 (82.6%)	–	–	
Yes	–	34 (17.4%)	–	–	
BMI (kg/m^2)	219	24 ± 4	19	26 ± 5	0.877
Diabetes durations (years)	–	–	252	20 ± 11	–
Duration of follow-up (years)	–	–	254	13 ± 8	–
HbA1c (%)	209	8.2 ± 2.1	204	7.8 ± 1.6	**0.004**
Creatinine (mg/dl)	188	0.83 ± 0.18	149	0.85 ± 0.32	0.658
Serum albumin (mg/dl)	41	4.3 ± 0.68	21	4.2 ± 0.57	0.989
Triglycerides (mg/dl)	192	98 ± 70	145	95 ± 92	0.649
Total Cholesterol (mg/dl)	198	189 ± 42	157	181 ± 36	**0.045**
LDL (mg/dl)	170	114 ± 39	143	107 ± 31	**0.115**
HDL (mg/dl)	180	55 ± 18	148	59 ± 17	0.432
SGOT (U/L)	190	19 ± 11	153	20 ± 10	0.748
SGPT (U/L)	189	21 ± 15	153	20 ± 10	**0.074**
GGT (U/L)	167	17 ± 13	124	18 ± 13	**0.142**
ALP (U/L)	116	107 ± 70	69	76 ± 42	**0.014**
Urea (mg/dl)	185	32 ± 10	131	31 ± 11	0.402
Sodium (mmol/l)	148	139 ± 11	99	139 ± 11	0.632
Potassium (mmol/l)	146	5.3 ± 11	101	4.5 ± 0.47	0.342
Calcium (mmol/l)	85	9.3 ± 0.73	59	9.2 ± 1.3	0.610
Phosphate (mmol/l)	71	3.6 ± 0.88	35	3.5 ± 1.1	0.573
Serum glucose (mg/dl)	147	197 ± 102	85	170 ± 87	**0.052**
Serum uric acid (mg/dl)	21	4.3 ± 1.6	32	4.4 ± 1.3	0.335
WBC	179	7079 ± 2197	126	7092 ± 2137	0.990
PLTs	164	256350 ± 92675	117	257262 ± 91859	0.772
TSH (mlU/L)	170	3.1 ± 8.0	107	2.4 ± 2.2	0.240
T3 (ng/dl)	123	69 ± 57	44	61 ± 58	0.828
T4 (μg/dl)	24	22 ± 34	7	52 ± 59	–
FT4 (ng/dl)	94	4.6 ± 5.5	68	4.5 ± 5.5	0.696
Thyroid disease					–
No	–	159 (64.6%)	–	–	
Yes	–	87 (35.4%)	–	–	

[a] Paired samples *t*-test.

intensive insulin management and at baseline they were educated for titration of basal insulin and for counting carbohydrates and correction boluses of rapid insulin. Patients were treated with RAAS inhibition and statins when indicated. Age, sex, duration of diabetes, duration of follow-up, smoking habits, BMI, data regarding diabetic retinopathy, ischemic heart disease, UAE levels and values of various biochemical parameters were recorded too.

Current smoking (yes, no), diabetic retinopathy (yes, no) after the expertized ophthalmologist examination, ischemic heart disease (yes, no) with regards to ECG, cardiac stress test and cardiac triplex were also recorded.

Waist circumference and height (without shoes) were measured to the nearest 0.5 cm, and weight was measured with a lever balance, to the nearest 100 g, without shoes, in light undergarments. Body Mass Index (BMI) was then calculated as weight in kilograms divided by the square of standing height in meters. Glucose, total cholesterol, high-density lipoprotein (HDL) low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid, creatinine, alanine-transferase (ALT), aspartate-transferase (AST), gamma-glutamyl-transferase (γGT), alkaline phosphatase (ALP), and thyroid hormone levels (T3, FT4, TSH) together with autoantibodies were measured, too.

3. Statistical analysis

Results are presented as mean values ± SD for the normally distributed continuous variables (ie., age, BMI, HbA1c, GFR, creatinine, LDL-cholesterol, HDL-cholesterol, total cholesterol, uric acid, etc) and as frequencies [N (%)] for the categorical variables (i.e., gender, physical activity, smoking, obesity status, drinking, retinopathy, etc). Normality was tested using graphical methods (i.e., P–P plots and histograms). The paired samples *t*-test was used for the analyses of the data. The non-parametrical Kruskal-Wallis criterion was used for the analyses of non-parametrical values. All statistical analyses were performed using the SPSS version 20.0 (IBM Co., Armonk, NY, USA). All reported P-values are two-tailed and P-values less than 0.05 were considered statistically significant.

4. Results

Characteristics of the participants are shown in Table 1. Of the 256 patients with type 1 diabetes, 150 participants (58.6%) were women and 106 (41.4%) were men. One hundred and fifty-nine patients (64.6%) did not have autoimmune thyroiditis, whereas 97 (35.4%) had autoimmune thyroiditis, as was documented by the presence of anti-thyroid antibodies (anti-TPO and/or anti-TG). Of the 97 patients with both diabetes type 1 and autoimmune thyroiditis, 64 (66%) were women and 33 (34%) were men. Among the 97 patients who had both diabetes type 1 and autoimmune thyroiditis, 87 had abnormal levels of both anti-TPO and anti-TG, while 7 patients had subnormal levels of solely anti-TPO and only 3 patients had abnormal levels of only anti-TG (see Fig. 1).

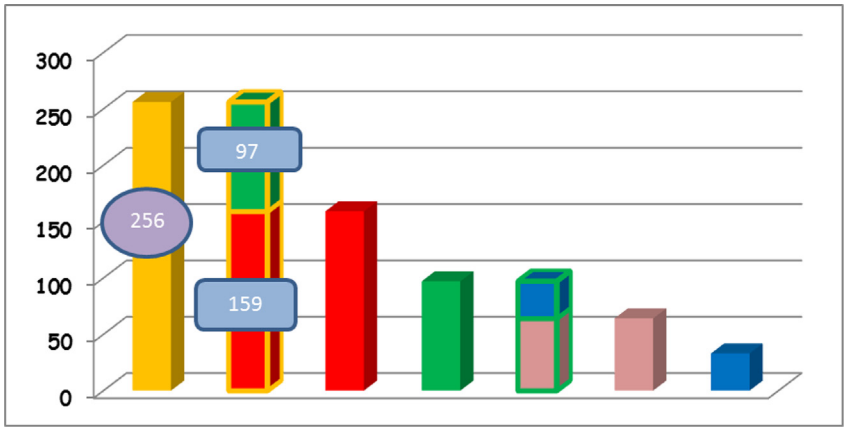

Fig. 1. Among the 256 participants with type 1 DM, 97 had abnormal anti-thyroid autoantibodies, while 159 had no detectable autoantibodies.
With the green color are the participants (number = 97), who had autoimmune thyroid disorders, while in red (number = 159) are those without thyroid autoimmune disease. Pink color depicts female patients with type 1 diabetes and AIT (number = 64), while blue column depicts male patients with type 1 DM and AIT (number = 33).

5. Discussion

The similar pathogenesis of type 1 DM and AIT together with their frequent clustering within families and individuals, suggest a potentially shared genetic etiology [1–4]. Human leukocyte antigen class II, cytotoxic T-lymphocyte antigen 4, and protein tyrosine phosphatase non-receptor type 22, have been suggested as "potential genetic susceptibility loci" [5–11]. Recently, a novel splice variant of FOXP3 lacking exon 6 has been identified, which is expressed in human thymus and lymph node. Notably, this splice variant was expressed in human regulatory T cells, suggesting it may play a role in their function [12].

Apart from the genetic susceptibility, it seems likely that age and female sex are implicated in the co-existence of both diseases [6–19]. In particular, among 233 Brazilian children and adolescents with type 1 diabetes, 23% had autoimmune thyroiditis, with the majority being female and older than 5 years age [6]. Another study, which enrolled 382 Polish children and adolescents with type 1 diabetes reported that 14.4% of the patients had elevated concentrations of antibodies against thyroid peroxidase [10]. In a nationwide study of children and adolescents with type 1 diabetes in Germany and Austria, showed that thyroid antibody levels were elevated amongst 1530 out of the 7097 patients (22%). Of the patients with positive antibodies, 63% were females [11]. In a recent review, androgens had a protective effect against the progression of autoimmunity, while estradiol seemed to accelerate the progression of this autoimmune disease through the T-lymphocytes pathway [15]. Besides, thyroid antibodies seem to be increased with age [11]. Moreover, in a study of 491 children from the Barbara Davis Center for Childhood Diabetes in Colorado 122 participants (24.8%) were positive for thyroid peroxidase autoantibodies [13]. A study consisting of 115 Korean adolescent patients with type 1 diabetes demonstrated a 25% prevalence of autoimmune thyroiditis in patients with type 1diabetes, compared with 8% in their age and sex-matched controls [17]. However, there was no statistical difference between female and male patients with type 1 DM in a recently reported study [20]. These differences may be due to differences in ethnic backgrounds as well as the study sample size [16–21]. Nevertheless, it seems likely that there is predominance among female patients when compared to male subjects. In our study, the development of AIT was increased among female patients comparing to male participants (66% versus 34%, respectively). Also, our study enrolled patients with type 1 DM, 18–79 years of age, ie not in the pediatric population, but in adults with type 1 DM. Therefore, the slightly increased prevalence of AIT (35.4%) among our participants may be due to the older age of the participants, who were enrolled in the study.

However, there are several limitations regarding our study. First, as the study was a retrospective one, there may be no causal associations, but just statistically significant observations. Second, no other autoimmune diseases, if there was any other co-existence, were recorded. Finally, we lacked GADA for every participant; therefore, we could not determine any potential relationship between the existence of GADA and anti-thyroid antibodies, as has been performed by other researchers [22–24]. However, among the strengths of our study is the long duration of follow-up, between 1987 and by the end of 2016.

In conclusion, there was a slightly higher prevalence of AIT among our patients with type 1 DM. Also, female sex was predominant when compared to male sex among the adult participants of this study. Therefore, regular screening of thyroid function and thyroid autoantibodies may be suggested for all patients with type 1 DM. Notably, the American Diabetic Association and International Society for Pediatric and Adolescent Diabetes recommend the screening of thyroid function and autoantibodies at the initial diagnosis, and the regular screening of thyroid function even in asymptomatic patients [25].

Conflicts of interest

There is no conflict of interest.

References

[1] Huber A, Menconi F, Corathers S, Jacobson EM, Tomer Y. Joint genetic susceptibility to type 1 diabetes and autoimmune thyroiditis: from epidemiology to mechanisms. Endocr Rev 2008;29:697–725.
[2] McKenna MJ, Herskowitz R, Wolfsdorf JI. Screening for thyroid disease in children with IDDM. Diabetes Care 1990;13:801–3.
[3] Kordonouri O, Klinghammer A, Lang EB, Gruters-Kieslich A, Grabert M, Holl RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care 2002;25(8):1346–50.
[4] Bright GM, Blizzard RM, Kaiser DL, Clarke WL. Organ-specific autoantibodies in children with common endocrine diseases. J Pediatr 1982;100:8–14.
[5] Villano MJ, Huber AK, Greenberg DA, Golden BK, Concepcion E, Tomer Y. Autoimmune thyroiditis and diabetes: dissecting the joint genetic susceptibility in a large cohort of multiplex families. J Clin Endocrinol Metab 2009;94(4):1458–66.
[6] Riquetto AD, de Noronha RM, Matsuo EM, Ishida EJ, Vaidergorn RE, Soares Filho MD, et al. Thyroid function and autoimmunity in children and adolescents with Type 1 Diabetes Mellitus. Diabetes Res Clin Pract 2015;110(1). e9-11.
[7] Chujo D, Foucat E, Nguyen TS, Chaussabel D, Banchereau J, et al. ZnT8-Specific

CD4+ T cells display distinct cytokine expression profiles between type 1 diabetes patients and healthy adults. PloS One 2013;8(2), e55595.
[8] Sardu C, Cocco E, Mereu A, Massa R, Cuccu A, et al. Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. PloS One 2012;7(3), e32487.
[9] Masala S, Cossu D, Palermo M, Sechi LA. Recognition of Zinc Transporter 8 and MAP3865c Homologous Epitopes by Hashimoto's Thyroiditis Subjects from Sardinia: a Common Target with Type 1 Diabetes? PloS One 2014;9(5), e97621.
[10] Piatkowska E, Szalecki M. Autoimmune thyroiditis in children and adolescents with type 1 diabetes. Pediatr Endocrinol Diabetes Metab 2011;17(4):173–7.
[11] Golden B, Levin L, Ban Y, Concepcion E, Greenberg DA, Tomer Y. Genetic analysis of families with autoimmune diabetes and thyroiditis: evidence for common and unique genes. J Clin Endocrinol Metab 2005;90:4904–11.
[12] Dissecting the role of the foxp3 gene in the joint genetic susceptibility to autoimmune thyroiditis and diabetes: a genetic and functional analysis. Gene 2015;556(2):142–8.
[13] Triolo TM, Armstrong TK, McFann K, Yu L, Rewers MJ, Klingensmith GJ, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. Diabetes Care 2011;34(5):1211–3.
[14] Karavanaki K, Kakleas K, Paschali E, Kefalas N, Konstantopoulos I, Petrou V, et al. Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (T1DM). Horm Res 2009;71:201–6.
[15] Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol 2014;35:347–69.
[16] Lorini R, d'Annunzio G, Vitali L, Scaramuzza A. IDDM and autoimmune thyroid disease in the pediatric age group. J Pediatr Endocrinol Metab 1996;9(Suppl 1):89–94.
[17] Park YS, Kim TW, Kim WB, Cho BY. Increased prevalence of autoimmune thyroid disease in patients with type 1 diabetes. Korean J Intern Med 2000;15(3):202–10.
[18] Tsirogianni A, Pipi E, Soufleros K. Specificity of islet cell autoantibodies and coexistence with other organ specific autoantibodies in type 1 diabetes mellitus. Autoimmun Rev 2009;8:687–91.
[19] Moriguchi M, Noso S, Kawabata Y, Yamauchi T, Harada T, Komaki K, et al. Clinical and genetic characteristics of patients with autoimmune thyroid disease with anti-islet autoimmunity. Metabolism 2011;60:761–6.
[20] Hwang GB, Yoon JS, Park KJ, Lee HS, Hwang JS. Prevalence of autoimmune thyroiditis in patients with type 1 diabetes: a long-term follow-up study. Ann Pediatr Endocrinol Metab 2018;23:33–7.
[21] Shun CB, Donaghue KC, Phelan H, Twigg SM, Craig ME. Thyroid autoimmunity in type 1 diabetes: systematic review and meta-analysis. Diabet Med 2014;31:126–35.
[22] Jung ES, Han DK, Yang EM, Kim MS, Lee DY, Kim CJ. Thyroid autoimmunity in children and adolescents with newly diagnosed type 1 diabetes mellitus. Ann Pediatr Endocrinol Metab 2014;19:76–9.
[23] Jin P, Huang G, Lin J, Yang L, Xiang B, Zhou W, et al. High titre of antiglutamic acid decarboxylase autoantibody is a strong predictor of the development of thyroid autoimmunity in patients with type 1 diabetes and latent autoimmune diabetes in adults. Clin Endocrinol (Oxf) 2011;74:587–92.
[24] Jonsdottir B, Larsson C, Carlsson A, Forsander G, Ivarsson SA, Lernmark Å, et al. Thyroid and islet autoantibodies predict autoimmune thyroid disease at type 1 diabetes diagnosis. J Clin Endocrinol Metab 2017;102:1277–85.
[25] American Diabetes Association. 12. Children and adolescents. Diabetes Care 2017;40(Suppl 1):S105–13.