*Rev Port Endocrinol Diabetes Metab. 2019;***14(1)**

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Original

Thyroid Autoimmunity in Patients with Type 1 Diabetes

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INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2017-12-29
Accepted/Aceite: 2018-12-02
Online: 2019-09-30

Keywords:
Autoimmunity
Diabetes Mellitus, Type 1
Thyroid Diseases
Thyroid Gland/immunology

A B S T R A C T

Introduction: Although with significant geographic differences, the prevalence of thyroid autoimmunity is higher in patients with type 1 diabetes. Female sex, age, and diabetes duration have been associated with higher risk of thyroid autoimmunity. We aim to evaluate, in our population of type 1 diabetes patients, the occurrence of thyroid autoimmunity and determine differences for age and gender.
Material and Methods: Retrospective study of laboratory results with clinical information on type 1 diabetes from the last 15 years in our hospital. Thyroid autoimmunity was defined by positive thyroid autoantibodies (thyroid peroxidase antibody and/or thyroglobulin antibody). Statistical analysis: IBM SPSS v. 20.
Results: We analyzed data from 554 type 1 diabetes patients, however, only 263 (47.5%) patients had at least one determination of thyroid auto-antibodies and were included for the analysis. The patients had a median age of 22.0 years (IQR 13.0-34.0). Most patients were adults (60.1%; n = 158) and females (56.7%; n = 149). Thyroid autoimmunity was present in 23.2% (n = 61) and there were no statistical differences in age ($p = 0.055$) or gender ($p = 0.310$).
Conclusion: Thyroid autoimmunity was present in almost one-quarter of type 1 diabetes patients, without statistical differences between gender and age. In contrast with previous studies that reported a higher prevalence in females, our study failed to demonstrate the female bias in thyroid autoimmunity occurrence.

Autoimunidade Tiroideia em Doentes com Diabetes Tipo 1

Palavras-chave:
Autoimunidade
Diabetes Mellitus Tipo 1
Doenças da Tiróide
Glândula Tiróide/imunologia

R E S U M O

Introdução: Embora com diferenças geográficas significativas, a prevalência de autoimunidade tiroideia é superior em doentes com diabetes tipo 1. Nestes doentes, o sexo feminino, a idade e a duração da diabetes têm sido associados a um risco superior de desenvolvimento de autoimunidade tiroideia. Os objetivos do estudo foram a avaliação, na nossa amostra de doentes com diabetes tipo 1, da ocorrência de autoimunidade tiroideia e determinar eventuais diferenças entre os doentes de acordo com a idade e o género.
Métodos: Estudo retrospetivo dos resultados laboratoriais com informação clínica de diabetes tipo 1 dos últimos 15 anos no nosso hospital. A autoimunidade tiroideia foi definida pela positividade de auto-anticorpos tiroideus (anticorpo anti-peroxidase e/ou anticorpo anti-tireoglobulina). Análise estatística: IBM SPSS v. 20.
Resultados: Foram analisados dados de 554 doentes com diabetes tipo 1, contudo apenas 263 (47,5%) doentes apresentavam determinação de auto-anticorpos tiroideus A idade mediana dos doentes foi 22,0 anos (IQR 13,0-34,0). A maioria dos doentes eram adultos (60,1%; n = 158) e do sexo feminino

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https://doi.org/10.26497/ao180036

(56,7%; n = 149). A autoimunidade tiroideia estava presente em 23,2% (n = 61) e não se verificaram diferenças estatisticamente significativas para a idade (p = 0,055) ou género (p = 0,31).
Conclusão: A autoimunidade tiroideia estava presente em quase um quarto dos doentes com diabetes tipo 1, contudo sem diferenças estatísticas entre o sexo e a idade. Ao contrário de estudos anteriores que reportaram maior prevalência em mulheres, o nosso estudo não demonstrou o viés feminino na ocorrência de autoimunidade tiroideia.

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder in which endogenous insulin production is severely compromised due to an immune-mediated injury of pancreatic beta cells. These patients have an increased risk of developing other autoimmune responses against other organs and/or tissues, particularly autoimmune thyroid disorders.[1] Autoimmune thyroid disorders are the most common autoimmune disorders, affecting 5% of the general population. They include two main clinical presentations – Hashimoto's thyroiditis and Graves disease.[2] Both forms are associated with antibody production against specific thyroid gland proteins and are characterized by lymphocytic infiltration of thyroid parenchyma.[3,4] Thyroid autoimmunity without clinical dysfunction, diagnosed by the presence of thyroid autoantibodies, is a unique phenotype of autoimmune thyroid disorders and is even more frequent.[4] Thyroid peroxidase antibodies (anti-TPO) are a sensitive marker of autoimmune thyroid disorders, both in Hashimoto's thyroiditis and Graves disease and of thyroid dysfunction. Thyroglobulin antibodies (anti-Tg) are less sensitive and less specific, reflecting a more initial type of immune response, whereas anti-TPO may characterize a later adaptive immune response, in a sort of immune escalation.[4,5] Antibody against the thyroid stimulating hormone (TSH) receptor (TRABs) are pathognomonic of Grave's disease and the stimulating form is responsible for the hyperthyroidism.[4]

There is a strong link between autoimmune thyroid disorders and T1DM as they frequently occur together in the same individual and in familiar clusters, suggesting a shared genetic susceptibility.[6] The prevalence of thyroid autoimmunity in patients with T1DM is two to four times more frequent than in the general population. The usual clinical presentation is HT and less frequently GD.[7] Both autoimmune thyroid disorders and T1DM are organ-specific T-cell-mediated diseases where endocrine glands are affected by autoantibodies, and in both disorders, T-cell infiltration occurs with subsequent dysfunction and destruction.[8] Epidemiological surveys that analyzed the co-occurrence of T1DM and autoimmune thyroid disorders showed significant geographic differences, although the prevalence of autoimmune thyroid disorders in these patients is always higher than in the general population. A greater risk is conferred by female gender, older age and longer duration of diabetes.[2,7,9] Up to 50% of T1DM had thyroid autoantibodies without thyroid dysfunction and half of these patients will progress to clinical autoimmune thyroid disorders.[7,10,11]

Despite the recognized risk of thyroid disease in T1DM and its potential for significant morbidity, there is no uniformity in the current guidelines for T1DM concerning recommendations for thyroid autoantibodies screening.[9]

So far, there is no published data on prevalence and characterization of thyroid autoimmunity in T1DM in our population. The main purposes of our study are the evaluation of thyroid autoimmunity frequency in T1DM, assessed by positive results of thyroid autoantibodies anti-TPO and/or anti-Tg. Additionally, we aim to analyze the presence of eventual differences for age and gender.

Material and Methods

Data sources and collection

This cross-section study was conducted in the Pathology Department in Hospital de Braga. We analyzed through *Clinidata software* the laboratory results between 30/11/2001 and 30/01/2016. We selected clinical information of T1DM with at least one result of glucose, glycosylated hemoglobin (HbA1c), thyroid stimulating hormone (TSH), thyroid peroxidase antibodies (anti-TPO) or thyroglobulin antibodies (anti-Tg). Age and gender at time of thyroid auto-antibodies determination were also documented.

We obtained 2665 laboratory results of 554 T1DM patients. However, only 263 patients had at least one determination of thyroid auto-antibodies (anti-TPO and/or anti-Tg) and included for the analysis. In the patients with more than one result of auto-antibodies, we selected the highest value.

We defined a control group by selecting patients without T1DM that had, in the same period, results of anti-TPO and/or anti-Tg (n = 964).

Laboratory assays

Glucose was measured using a glucose oxidase method. HbA1c was measured using high-performance liquid chromatography (HPLC) with Variant™ Hemoglobin A1c Program (Bio-Rad Laboratories, Hercules, CA, USA) and Tosoh G7 Automated HPLC Analyzer. Throughout the study period, quantitative levels of anti-TPO and anti-Tg were measured by quimioluminescent assay (Immulite® 2000, Siemens). Levels of anti-TPO below 35 UI/mL and anti-Tg below 40 UI/mL were considered normal. Serum TSH (normal values between 0.358 and 3.74 uUI/mL) concentration was measured by quimioluminescent assay (Immulite® 2000, Siemens).

Definition of thyroid autoimmunity

We defined thyroid autoimmunity if patients had positive results of anti-TPO and/or anti-Tg. According to this, the patients were divided into two groups - with or without thyroid autoimmunity.

Statistical analysis

All continuous variables analyzed had a non-normal distribution and were expressed as median and interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. Group comparisons were made using the Mann–Whitney U test for continuous variables with non-normal distribution and the chi-square ($\chi 2$) test for categorical variables.

Statistical significance was defined at $p < 0.05$. Trend to statistical significance was defined if $p > 0.05$ and < 0.1. Statistical analysis was performed using IBM SPSS™ software version 20.

Results

Of the initial population of 554 T1DM patients, we included 263 T1DM patients for the analysis with a median age was 22.00

Table 1. Clinical characteristics between patients with and without thyroid autoimmunity

Variables	TA	Without TA	*p* value
Age (years), median (IQR)	25.0 (15.0 - 33.0)	20.50 (11.0 - 34.0)	0.055
Patients < 18 / ≥ 18 years , % (n)	31.1 (19) 68.9 (42)	42.6 (86) 57.4 (116)	0.110
Gender, % (n)	M: 20.2 (23) F: 25.5 (38)	M: 79.8 (91) F: 74.5 (111)	0.310
A1c (%), median (IQR)	9.0 (8.0 - 10.25)	9.0 (8.0 - 11.0)	0.832
TSH (uUI/ml), median (IQR)	4.0 (2.0 - 6.0)	3.0 (2.0 - 3.0)	< 0.001

TA: thyroid autoimmunity; IQR: interquartile range; M: male; F: female; A1c: glycosylated hemoglobin; TSH: thyroid stimulating hormone

(IQR 13.0-34.0). Most patients were female (n = 149; 56.7%) and adults (n = 158; 60.1%).

Thyroid autoimmunity was present in 23.2 % (n = 61) of the patients with T1DM. The detailed characteristics of the patients are described in Table 1.

A trend to higher age in patients with thyroid autoimmunity was revealed, although without statistical significance (25.0 *vs* 20.5; $p = 0.055$).

There was no association between frequency of thyroid autoimmunity and gender ($p = 0.310$). However, in the control group, as described in Fig. 1, there was a predominance of females in patients with thyroid autoimmunity ($p < 0.001$).

No statistical differences in thyroid autoimmunity frequency were demonstrated between pediatric and adult patients (18.1% *vs* 26.6%; $p = 0.110$).

Also, as described in Table 2, the separate analysis between age groups revealed no statistical differences in thyroid autoimmunity prevalence between genders in adults or pediatric patients $p= 0.306$ and $p = 0.797$, respectively.

Discussion

In our study, 23.2% of patients with T1DM had thyroid autoimmunity. This prevalence is in agreement with cross-sectional studies in which the prevalence of thyroid autoimmunity range from 10% to 33%.[9]

We did not find a higher prevalence of thyroid autoimmunity in adults as reported in some studies, based on the concept that thyroid autoimmunity in T1DM is a phenomenon of late onset, with a peak around puberty.[9,12] However, the difference in age between patients with and without thyroid autoimmunity almost reach statistical significance (25.0 *vs* 20.5; $p = 0.055$). The sample size of our study may be an explanation for the absence of statistical differences between the groups.

Our results revealed no differences in thyroid autoimmunity prevalence in males or females with T1DM, in contrast with the control group (without T1DM) where a predominance of females in patients with thyroid autoimmunity was documented. It has been suggested that female gender is a risk factor for thyroid autoimmunity and several studies reported a higher prevalence of thyroid autoimmunity in female patients with T1DM.[12–15] However these studies are mainly in children and adolescents and, the data on thyroid dysfunction is variable.[9] A recent study of T1DM patients from Netherlands reported higher prevalence in women of positive thyroid auto-antibodies (anti-TPO positive and anti-Tg).[16]

Jonsdottir *et al* also report a higher frequency of thyroid autoimmunity in girls, however, the girl/boy ratio in children and adolescents with T1DM is decreased compared to the general popula-

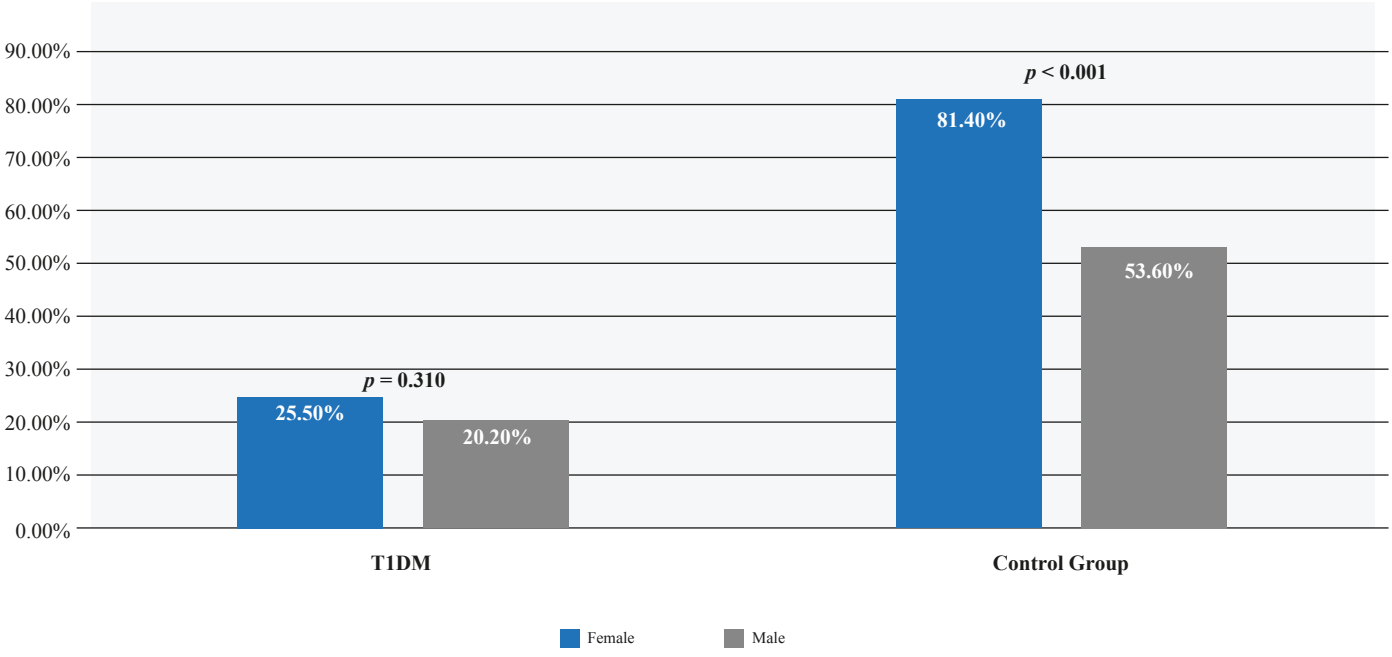

Figure 1. Gender differences in occurrence of thyroid autoimmunity

Table 2. Gender differences in thyroid autoimmunity according to age

	Pediatric age (< 18 years) (n=105)				Adults (≥ 18 years) (n=158)			
TA, % (n)	**All**	**Males**	**Females**	***p* value**	**All**	**Males**	**Females**	***p value***
	18.1 (19)	17.0 (8)	19.0 (11)	0.797	26.6 (42)	22.4 (15)	29.7 (27)	0.306

TA: thyroid autoimmunity

tion and the authors conclude that the relative risk for a boy with T1DM to develop autoimmune thyroid disorders is higher.[17]

The absence of female preponderance in our study may, in part, be explained by the sample size. Moreover, the absence of gender differences in thyroid autoimmunity frequency may be explained by a possible loss of protection of thyroid autoimmunity in males with T1DM.

An interesting point in this analysis was the absence of autoantibodies determination in more than half of the T1DM patients. These results may demonstrate the lack of consistency amongst current follow-up screening recommendations. Currently, the American Diabetes Association recommends screening for anti-TPO, anti-Tg and TSH at T1DM diagnosis. According to this recommendation, if normal, TSH recheck should be considered every 1 to 2 years or more frequently if the patient develops unusual glycemic variation or symptoms of thyroid dysfunction or thyromegaly.[18] The International Society for Pediatric and Adolescent Diabetes recommends screening with TSH and anti-TPO at diagnosis of T1DM and thereafter every second year in asymptomatic individuals without goiter or in the absence of thyroid autoantibodies, while no specific recommendations on how children with thyroid autoimmunity should be followed are given.[19]

Targeted screening for thyroid dysfunction in patients with thyroid autoimmunity at T1DM diagnosis may be more frequent due to the high positive predictive value of thyroid autoantibodies for autoimmune thyroid disease. However, more data is needed on the rate of progression to clinical disease to inform about appropriate screening intervals.[9]

Limitations

An important limitation of this study was the sample size. The authors considered that this may have compromised the absence of statistical differences between the groups. Also, as thyroid auto-antibodies determinations were only available in 47.5% of patients of this cohort, the total prevalence of thyroid autoimmunity might be underestimated.

This study analyzed the prevalence of thyroid autoimmunity in T1DM patients retrospectively and we did not evaluate long-term outcomes as progression to thyroid dysfunction. In addition, we do not have data of age at diagnosis and duration of T1DM, genetic predisposition or family history of the patients.

Another limitation was the control group selection. This group was composed by the patients without T1DM that had, in the same period, results of anti-TPO and/or anti-Tg. In this group the prevalence of thyroid autoimmunity was high and the authors admit a possible selection bias prevalence.

Conclusion

Thyroid autoimmunity is present in almost one-quarter of T1DM patients, without statistical differences in prevalence according to age and gender. Although female gender is considered a risk factor for thyroid autoimmunity, our study failed to demonstrate a female bias.

Ethical Disclosures

Conflicts of Interest: The authors report no conflict of interest.
Funding Sources: No subsidies or grants contributed to this work.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

Responsabilidades Éticas

Conflitos de interesse: Nenhum na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

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