

# Thyroid disorders are common in first-degree relatives of individuals with type 1 *diabetes mellitus*

Débora Batista Araujo<sup>1</sup>, Bianca Barone<sup>2</sup>, Natasha Ferreira Teixeira Melleti<sup>1</sup>, Joana Rodrigues Dantas<sup>1</sup>, Marcus Miranda dos Santos Oliveira<sup>1</sup>, Lenita Zajdenverg<sup>1</sup>, Rosangela Prendim Tortora<sup>3</sup>, Mario Vaisman<sup>4</sup>, Adolpho Milech<sup>1</sup> José Egídio Paulo de Oliveira<sup>1</sup>, Melanie Rodacki<sup>1</sup>

<sup>1</sup> Department of Internal Medicine, Diabetes and Nutritional Diseases Section, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil

<sup>2</sup> State Institute of Diabetes and Endocrinology Luiz Capriglione (IEDE), Rio de Janeiro, RJ, Brazil

<sup>3</sup> Department of Internal Medicine, Immunology Section, UFRJ, Rio de Janeiro, RJ, Brazil

<sup>4</sup> Department of Internal Medicine, Endocrinology Section, UFRJ, Rio de Janeiro, RJ, Brazil

## Correspondence to:

Débora Batista Araujo de Pina Cabral  
Av. Epitácio Pessoa, 2990, ap. 806  
22471-003 – Rio de Janeiro, RJ, Brazil  
dbatistaaraujo@gmail.com

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## ABSTRACT

**Objective:** Thyroid diseases are common in individuals with type 1 *diabetes mellitus* (T1DM) and should be investigated annually in these individuals. The aim of this study was to evaluate the frequency of thyroid diseases in first degree relatives (FDR) of patients with T1DM. **Subjects and methods:** Eighty individuals (40 patients with T1DM and 40 FDR) were interviewed and blood was sampled for thyroid-stimulating hormone (TSH), free thyroxine (FT4) and thyroid peroxidase (TPO) antibodies measurement. Autoantibodies against glutamic acid decarboxylase 65 (GAD65), islet antigen-2 (IA2) and autoantibodies against insulin (AAI) were measured in FDR. **Results:** We found a similar prevalence of thyroid dysfunction in patients with T1DM and their FDR (22.5% vs. 27.5%;  $p = 0,79$ ). There were no differences in serum TSH levels ( $p = 0,29$ ), FT4 ( $p = 0,45$ ), frequency of abnormal TSH ( $p = 0,28$ ), positive TPO antibodies ( $p = 0,13$ ), titers of TPO antibodies (in positive cases) between patients with T1DM and their FDR ( $p = 0,94$ ). **Conclusions:** Thyroid abnormalities seem to be common not only in patients with T1DM but also in their FDR, which suggests that screening strategies for thyroid diseases might also be useful to these individuals. Arch Endocrinol Metab. 2015;59(2):112-5

## Keywords

Autoimmunity; diabetes; thyroid dysfunction

## INTRODUCTION

Patients with type 1 *diabetes mellitus* (T1DM) are at increased risk for other autoimmune disorders, such as autoimmune thyroid disease (ATD), celiac disease and Addison's disease (1-3). The most prevalent autoimmune disease in patients with T1DM is ATD. Although quite a variable frequency of thyroid antibodies (thyroglobulin antibody – TgAb and thyroid peroxidase antibody – TPOAb) and thyroid dysfunction (TD) has been reported in patients with T1DM among different populations (from 3 to 50%), a high prevalence of ATD has been reported in most cases. This suggests that both diseases share etiopathogenic mechanisms (2-6). Current guidelines recommend that all patients with T1DM should undergo an annual screening for thyroid disease with at least a serum TSH measurement (2,6-8).

Clustering of autoimmune disorders is commonly observed in families of patients that have autoimmu-

ne diseases. Previous studies have shown that first degree relatives (FDR) of patients with T1DM have an increased prevalence of thyroid abnormalities than the general population (2,3,9-12), ranging from 8 to 25% (2,3). However, these studies have included mostly Caucasians, very little is known about the prevalence of ATD in other ethnic groups and thyroid disease often remains undiagnosed in this group (12,13). The aim of this study was to investigate the frequency of thyroid diseases and thyroid autoimmunity in FDR of patients with T1DM from the Brazilian multiethnic population.

## SUBJECTS AND METHODS

Eighty individuals were enrolled in this study, 40 patients with T1D (group 1) and their respective FDR (group 2). Patients were randomly selected, in order of appearance. All patients were followed at the Dia-

betes and Nutritional Diseases Section at Clementino Fraga Filho University Hospital (HUCFF) of Federal University of Rio de Janeiro (UFRJ), and at the State Institute of Diabetes and Endocrinology Luiz Capriglione (IEDE) in Rio de Janeiro, Brazil. The project was approved by the institutional review board and all participants signed an informed consent.

T1D was defined according to the American Diabetes Association criteria. One participant per family was included, and they were siblings or children of the index patient.

All subjects were interviewed and blood was sampled for thyroid stimulating hormone (TSH), free thyroxine (FT4) and thyroid peroxidase (TPO) antibodies measurement. Autoantibodies against glutamic acid decarboxylase 65 (GAD65), islet antigen-2 (IA2A) and autoantibodies against insulin (IAA) were also measured in the FDR. Thyroid dysfunction was defined by the presence of abnormal TSH levels and/or previous known thyroid disorder.

Serum TSH and TPO antibody were measured with a Chemiluminescence method according to the manufacturer's instructions (Immulite – Diagnostic Products Corporation). For FT4, GADA, IA2A and IAA antibodies a direct radiobinding assay (Immulite-Diagnostic Products Corporation) was used. All analyses were performed at Clementino Fraga Filho University Hospital, Rio de Janeiro, Brazil. The sera were stored at  $-80^{\circ}\text{C}$  degrees after sampling. Cut-off values for the test were set to  $0.4 - 4.0 \mu\text{IU/mL}$  for TSH,  $0.8 - 1.8 \text{ ng/dl}$  for FT4,  $> 35 \text{ UI/mL}$  for the positive TPO antibody, and  $\geq 1.0 \text{ UI/ml}$  for positive GADA, IA2A and IAA antibodies.

All statistical analyses were performed using the Statistical Package for Social Science (SPSS). Mann-Whitney U test and Chi-Square were used for comparison between groups. A  $p$ -value  $< 0.05$  was considered significant.

## RESULTS

### Characteristics of the study group

Among T1DM patients and their FDR, there was a higher prevalence of women ( $57.5\%$  vs.  $70\%$ , respectively) and Whites ( $62.5\%$  vs.  $60\%$ , respectively). T1DM subjects were older than their FDR ( $30.83 \pm 10.57$  years vs.  $19.45 \pm 9.77$  years, respectively). In patients, the mean duration of diabetes was  $13.1 \pm 7.5$  years. The characteristics of the study group are shown in table 1.

**Table 1.** Epidemiological characteristics and prevalence of thyroid disorders in type 1 diabetes (T1D) patients and their first degree relatives (FDR)

Characteristics	T1D patients n = 40 (%)	FDR n = 40 (%)	p value
Gender			
Female	23 (57.5)	28 (70)	0.11
Ethnicity			
Whites	25 (62.5)	24 (60)	0.20
Non whites	15 (37.5)	16 (40)	
Age (mean $\pm$ SD years)	$30.83 \pm 10.57$	$19.45 \pm 9.77$	0.99
TSH level ( $\mu\text{I U/ml}$ ) (mean $\pm$ SD)	$2.32 \pm 1.78$	$3.57 \pm 4.35$	0.29
FT4 level (ng/dl) (mean $\pm$ SD)	$1.24 \pm 0.22$	$1.25 \pm 0.17$	0.45
TPOAb frequency (%)	14 (35)	7 (17.5)	0.13
TPOAb titers (U/ml) (mean $\pm$ SD)	280.64	306.14	0.94
Abnormal TSH level frequency (%)	7 (17.9)	12 (29.4)	0.28
Thyroid dysfunction (abnormal TSH and FT4 levels) frequency (%)	9 (22.5)	11 (27.5)	0.79
TSH level $\geq 2.5$ ( $\mu\text{I U/ml}$ )	13 (33.3)	15 (37.5)	0.81

T1D: type 1 diabetes; FDR: first degree relatives; TSH: thyroid-stimulating hormone; FT4: free thyroxine; TPOAb: thyroid peroxidase antibody.  
P-value  $< 0.05$  was considered significant.

### ATD in T1DM patients and their FDR

The prevalence of thyroid dysfunction (altered TSH and/or previous known thyroid disorder) did not differ between the groups ( $22.5\%$  x  $27.5\%$ ;  $p = 0.79$ ). A total of 8 subjects had primary hypothyroidism and were treated with levothyroxine (five patients and three FDR). These FDR had previous thyroid disease. In two of them, the correspondent index case with T1DM also had hypothyroidism. The prevalence of TSH levels  $\geq 2.5 \mu\text{IU/ml}$  was also similar in both groups ( $33.3\%$  vs.  $37.5\%$  respectively,  $p = 0.81$ ).

There were no significant differences in serum TSH levels ( $p = 0.29$ ), FT4 ( $p = 0.45$ ), abnormal TSH ( $p = 0.28$ ), positive TPO antibodies ( $p = 0.13$ ) and titers of TPO antibodies (in positive cases) between patients with T1DM and their FDR ( $p = 0.94$ ). Abnormal TSH levels were observed in patients and their FDR, as shown in table 1, and were independent of TPO antibody status ( $p = 0.67$ ). FT4 levels were normal in all patients with high TSH levels.

We found no association between TSH levels and gender ( $p = 0.31$ ), ethnicity ( $p = 1.00$ ) or age ( $p = 0.08$ ) in the group as a whole or with the positivity for

pancreatic autoantibodies (GADA  $p = 1.00$ , IA2A  $p = 0.49$  and IAA  $p = 1.00$ ) in the FDR.

The prevalence of GADA in FDR was 17.5% ( $n = 7$ ). There was a positive association between positive titers of GADA, positive TPO antibodies ( $p = 0.00$ ), and abnormal TSH levels ( $p = 0.01$ ).

## CONCLUSIONS

In this study, we identified a similar frequency of thyroid dysfunction and autoimmunity in patients with T1DM and their FDR. Current guidelines indicate that thyroid disorders should be screened annually in individuals with T1DM based on the high risk of the development of these abnormalities (14-16). Our data suggests that a significant proportion of FDR also develop thyroid autoimmunity and thyroid dysfunction.

Thyroid diseases may present with non-specific signs and symptoms and may remain undiagnosed for long periods of time. Untreated thyroid diseases may increase the risk of cardiovascular diseases through inter-relationships with dyslipidemia, insulin resistance and vascular endothelial dysfunction (17,18). Therefore, it is probable that FDR of patients with T1DM would also benefit by the current screening strategy for thyroid diseases that are applied for patients with T1DM.

Although we did not find any case of undiagnosed overt hypothyroidism in this study, subclinical hypothyroidism was quite common. There is increasing evidence of the role of subclinical asymptomatic hypothyroidism in the risk for cardiovascular diseases (17-19) and even TSH levels between 2.5 and 4.0 mU/liter have been linked to cardiovascular risk. The National Academy of Clinical Biochemistry has suggested that the cutoff for TSH levels should be  $< 2.5$  mU/liter, based on the observation that 95% of the normal population has TSH levels within this range (20). In this study, we did not find any difference in the proportion of individuals with TSH levels  $< 2.5$  mU/liter in patients with T1DM and FDR.

Although this study had a modest sample size, other small studies have identified similar results (2,3,9,19,21-24), including one in another sample of the Brazilian population (12). According to these authors, thyroid autoantibodies occur in 8% to 25% of FDR of T1DM patients. The prevalence of thyroid dysfunction is also high in this group (25%), being similar to the prevalence found in patients. These data confirm the high frequency of thyroid abnormalities in FDR of patients with T1DM and reinforce the relevance of investiga-

ting thyroid disorders in family members of individuals with T1DM.

This study has also other limitations, besides its size. First, an ultrasound of the thyroid gland was not performed. Moreover, only one measurement of TSH was performed for each individual, without a confirmation of the TSH levels above the reference range. In addition, this was a cross-sectional study and information about the proportion of first degree relatives of patients with T1DM that develop clinical thyroid disease over the years is still lacking.

We did not observe any characteristic that would help to identify the FDR of T1DM that are at an increased risk of thyroid abnormalities (age, gender, family member with ATD, positive GADA, IA2 or IAA). However, some authors have found a positive association between GADA and ATD (2,3,7,10,22-25). Bonifacio and cols. found a positive association between the risk of developing TPOAbs and the presence of GADA, whereas IA2A and IAA were not associated with TPO-Ab risk in relatives of T1DM patients.

Further larger longitudinal studies are necessary to clarify if a universal screening for thyroid diseases should be recommended for FDR of patients with T1DM or if there are clinical or immunogenetic characteristics that could identify the individuals that are more prone to develop thyroid dysfunction and who should therefore undergo this investigation.

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