Prevalence of thyroid-related abnormalities in adults with celiac disease: a cross-sectional study

Prevalência de alterações da tireoide em adultos com doença celíaca

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Revista HCPA. 2013;33(2):120-126

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ABSTRACT

BACKGROUND: An increased prevalence of autoimmune disorders, including thyroid diseases, has been reported in patients with celiac disease (CD). This study aimed to identify the prevalence of thyroid-related abnormalities in adults with CD.

METHODS: Thirty-nine subjects with biopsy-proven CD, three men (7.7%) and 36 women (92.3%), answered a questionnaire. All patients were followed at the outpatient clinic of Hospital de Clínicas de Porto Alegre. Thyroid-related abnormalities were evaluated by serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and anti-thyroperoxidase antibodies (anti-TPO) levels.

RESULTS: Three subjects had grade 1 lesions; one had grade 2; 13 had grade 3a; eight had grade 3b; and 14 had grade 3c, according to the modified Marsh classification. Mean age was 50.8 ± 12.9 years. Twenty-nine (74.4%) subjects were euthyroid. Ten subjects (25.6%) had hypothyroidism: eight of them (20.5%) were already taking levothyroxine, and subclinical hypothyroidism was identified during the study in the other two patients (5.1%). No patients were hyperthyroid. Mean serum FT4 levels were 1.15 ± 0.25 ng/dl. Median serum TSH levels were 2.39 (0.06-6.64)IU/ml. Serum anti-TPO levels were positive in six patients (15.4%): one with hypothyroidism, one with subclinical hypothyroidism, and four with normal thyroid function. No factors associated with thyroid-related abnormalities were identified.

CONCLUSION: This study showed a high prevalence of thyroid-related abnormalities, as did other studies. Since anti-thyroid antibodies were positive in some patients with normal thyroid function, periodic evaluation of thyroid function in CD patients is recommended.

Keywords: Celiac disease; gluten; autoimmune thyroid disease; prevalence

RESUMO

INTRODUÇÃO: Tem-se observado um aumento na prevalência de doenças auto-imunes, incluindo doenças da tireoide, em pacientes com doença celíaca (DC). O objetivo deste estudo foi identificar a prevalência de alterações da tireoide em adultos com DC.

MÉTODOS: Trinta e nove indivíduos com diagnóstico comprovado de DC, três homens (7,7%) e 36 mulheres (92,3%), responderam a um questionário. Todos os pacientes foram acompanhados no ambulatório do Hospital de Clínicas de Porto Alegre, alterações relacionadas à tireoide foram detectadas por meio da medição dos níveis de hormônio estimulador da tireoide (TSH), tiroxina livre (T4 livre) e

anticorpos antitireoperoxidase (anti-TPO), no soro.

RESULTADOS: Três pacientes apresentavam lesões tipo 1; um paciente apresentava tipo 2; 13 pacientes, tipo 3a; oito pacientes, tipo 3b; e 14 tipo 3c, de acordo com a classificação modificada de Marsh. A média de idade foi de 50,8 ± 12,9 anos. Vinte e nove (74,4%) pacientes apresentaram tireoide nomal. Dez indivíduos (25,6%) apresentaram hipotireoidismo: oito pacientes (20,5%) já usavam levotiroxina e dois pacientes (5,1%) com hipotireoidismo subclínico foram identificados durante a avaliação. Nenhum paciente apresentou hipertireoidismo. Os níveis médios séricos de T4L foram 1,15 ± 0,25 ng/dl. A mediana do TSH sérico foi 2,39 (0,06-6,64) UI/ml. Níveis séricos de anti-TPO foram positivos em seis pacientes (15,4%), um com hipotireoidismo, um com hipotireoidismo subclínico e quatro com função tireoidiana normal. Não se identificou fator associado a anormalidades relacionadas à tireoide.

CONCLUSÃO: Este estudo demonstrou uma alta prevalência de anormalidades tireoidianas, como observado em outros estudos. Uma vez que os anticorpos antitireoide estavam presentes em alguns pacientes com função tireoidiana normal, recomenda-se a avaliação periódica da função tireoidiana em pacientes com DC.

Palavras-chave: Doença celíaca; glúten; doenças autoimunes da tireoide; prevalência

Celiac disease (CD) is a small intestine disorder triggered by gluten proteins found in wheat, barley, and rye (1). It is a worldwide disorder, more common in Western countries; in Europe and in the United States, the prevalence of CD is 1% (2,3). Celiac individuals are genetically predisposed to developing the disease, specially when under the right environmental conditions (4). CD is considered a multi-organ condition, linked to a number of diseases, including autoimmune diseases (1,3,5).

The age of onset may vary (6). CD has a wide clinical spectrum, ranging from malabsorption syndrome to extraintestinal manifestations, and it can be atypical or even asymptomatic (7). Serological tests are useful for screening. The diagnosis is confirmed by histological abnormalities.

CD's association with autoimmune disorders causes increased morbidity and mortality. The risk of autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease, is much higher in celiac patients (3). Moreover, it has been shown that 14 to 30% of adults with CD may have autoimmune thyroid disease (ATD) (8).

Acknowledgment of the link between CD and ATD is important for disease management. Untreated autoimmune diseases, such as ATD, may cause high morbidity among celiac patients. Also, untreated CD may interfere with the course of other autoimmune diseases (9). For instance, when type 1 diabetes mellitus and CD coexist, treatment of CD improves glucose control, which reinforces the need to follow a gluten-free diet (GFD) (9). In patients with Hashimoto's thyroiditis or Graves' disease, an inadequate response to treatment may indicate the presence of CD (9).

A study by Elfström et al. showed a significant risk of increased hyperthyroidism in CD (3).

Hakanen et al. showed that 10-15% of celiac patients had positive antithyroid antibodies, which suggests that the prevalence of subclinical forms of ATD may be even higher (10). Nevertheless, the significance of anti-thyroperoxidase (anti-TPO) positivity is still unclear when thyroid function tests are normal (10).

Since the prevalence of CD and thyroid-related abnormalities is linked to genetic and environmental factors, the aim of this study was to identify the prevalence of thyroid-related abnormalities in adult patients with CD followed at the outpatient clinic of Hospital de Clínicas de Porto Alegre, in southern Brazil.

METHODS

A total of 1.276 duodenal biopsies were performed in the Hospital de Clínicas de Porto Alegre, Brazil, from January 2007 to May 2009 (29 months).We went over all the pathology tests results. We selected 165 biopsies, all of which showed some abnormality possibly related to CD, such as increased intra-

epithelial lymphocytes, villous hyperplasia, or atrophy. After that, we analyzed all 165 patients' records. Fifty-six of them were diagnosed with CD by their physicians. Six patients refused to participate in this study for different reasons, mostly because they lived far from the hospital; one patient was deceased; and 17 patients could not be reached. We included seven patients obtained by convenience sampling. The final sample was composed of 39 patients.

Trained physicians diagnosed CD based on clinical findings and/or positivity in serologic auto-antibodies, and histological criteria. Severity of CD was ranked using the Marsh classification. Adulthood was defined as beginning at age 18.

Specimens of intestinal mucosa were obtained through upper gastrointestinal endoscopy. Histological criteria were revised by two pathologists, both experts on CD, and classified into types 1, 2, 3a, 3b, and 3c (11,12), according to the Marsh-Oberhuber classification.

All data on associated diseases were obtained from interviews and electronic medical records. All subjects were submitted to a standard interview We collected data regardingdemographics, clinical findings, compliance with GFD, symptoms, and serologic data (thyroid function tests and anti-thyroperoxidase antibodies)for each patient. We onlyrecorded diseases described as CD-related in medical literature: iron deficiency anemia, lactose intolerance, anemia due to folic acid deficiency, osteopenia and osteoporosis, type 1 diabetes mellitus, dermatitis herpetiformis, and IgA deficiency.

We collected blood samples from each subject. Blood was immediately centrifuged at 4000×g for 10 minutes. Serum was assayed for anti-TPO (normal range: less than 34 IU/ml; intra- and inter-assay coefficient of variation, respectively, 6.3% and 9.5%), TSH (normal range: 0.27 to 4.2 IU/ml; intra- and inter-assay coefficient of variation, respectively, 3.0% and 7.2%), and free T4 (FT4) (normal range: 0.93 to 1.70 ng/dl; intra- and inter-assay coefficient of variation, respectively, 2.0% and 4.8%) levels. Chemiluminescence was performed using commercial kits (Roche Diagnostics, Mannheim, Germany).

Thyroid function was classified according to the American Thyroid Association (13). Overt hyperthyroidism was defined by a decrease in serum TSH levels and an increase in serum FT4 levels; subclinical hyperthyroidism was defined by decreased serum TSH levels and normal serum FT4 levels; overt hypothyroidism was defined by an increase in serum TSH levels and a decrease in serum FT4 levels; and subclinical hypothyroidism was defined by an increase in serum TSH levels with normal serum FT4 levels. Subjects were diagnosed with euthyroid autoimmune thyroid disease when anti-TPO was above 34 UI/mL with normal thyroid function.

We performed thestatistical analysis using SPSS 17.0. Variables with parametric distribution were presented as mean ± standard deviation (SD) or percentage (%), as appropriate. Variables with non-parametric distribution were shown as median and interquartile range. We used chi-square tests to evaluate associations between categorical variables. Differences in means between groups were evaluated using the t-test or the Mann-Whitney test according to data distribution. Two-tailed p values <0.05 were considered to be statistically significant.

All participants signed a written consent before joining the study, which was approved by the local ethics committee.

RESULTS

Thirty-nine patients with CD, 36 women (92.3%) and 3 men (7.7%), were included: three patients had grade 1 lesions; one had grade 2; 13 had grade 3a; eight had grade 3b; and 14 had grade 3c, according to the modified Marsh classification. Mean age was 50.8 ± 12.9 years. Out of 39 patients, 29 (74.4%) were euthyroid. Ten subjects (25.6%) had thyroid dysfunctions: two (5.1%) had subclinical hypothyroidism, and eight (20.5%) were taking levothyroxine for clinical hypothyroidism. No patient was hyperthyroid.

Seventeen (43.6%) patients were on a strict GFD, while 13 (33.3%) followed it often and five (12.8%) eventually followed the prescribed diet. Four (10.2%) patients never eliminated gluten from their diet.

Tables 1 and 2 summarize the demographic data of celiac patients with and without thyroid-related abnormalities. The associated comorbidities are shown in Table 3.

Six patients (15.4%) had positive anti-TPO antibodies: one with hypothyroidism, one with subclinical hypothyroidism, and four with normal thyroid function. The prevalence of thyroid-related

abnormalities was 35.9% (14 subjects) in the studied group. Mean serum FT4 levels were 1.15 ± 0.25 ng/dl; median TSH levels were 2.4 (0.1-6.6) IU/ml, and median anti-TPO levels were 8.1 (5.0-44.17) IU/ml.

Table 1: Characteristics of celiac disease (CD) patients with and without normal thyroid function.

Characteristics	Thyroid dysfunction (TD) (n=10)	Normalthyroid function (n=29)	p
Female [n(%)]	10 (100)	26 (89.7)	0.29
Patients on a GFD [n(%)]	3 (30)	14 (48.3)	0.31
Family history of CD [n(%)]	1 (10)	3 (10.3)	0.97
Family history of TD [n(%)]	5 (50)	12 (41.4)	0.63
Smoking [n(%)]	1 (10)	2 (6.9)	0.75
Pregnancies [n(%)]	2 (20)	5 (19.2)	0.67
Age (years)	53.3±14.5	49.9±12.8	0.48
Duration of CD (years)	5.0 (2.75-11.50)	5.0 (2.00-9.00)	0.68
Age of onset of CD (years)	45.9±17.9	44.5±12.1	0.78
BMI	23.58 ± 2.96	24.81 ± 3.82	0.36
Duration of GFD (years)	4.0 (2.0-11.50)	5.00 (2 - 9)	0.91
Duration of TD treatment (years)	4.0 (0.75-8.50)	-	-
TSH (mU/L)	4.4 (2.7-5.3)	2.2 (1.7-2.7)	0.009
Anti-TPO (IU/ml)	8.3 (5-46.1)	7.8 (5-13.5)	0.53
FT4 (ng/dL)	1.14±0.28	1.16±0.24	0.89

Thyroid dysfunction (TD): hypothyroidism (all taking levothyroxine) and subclinical hypothyroidism; GFD: gluten-free diet; BMI: body mass index; TSH: thyroid-stimulating hormone; TPO: thyroperoxidase; FT4: free thyroxine.

Data are shown as number (n) and percentage (%), mean± standard deviation, and median (P25/P75).

Table 2: Characteristics of celiac disease (CD) patients with and without thyroid-related abnormalities (hypothyroidism, subclinical hypothyroidism or euthyroid autoimmune thyroid disease).

Characteristics	Group		p
	Thyroid-related abnormalities (n=14)	No Thyroid-related abnormalities (n=25)	
Female [n(%)]	14 (100)	22 (88)	0.25
Patients on a GFD [n(%)]	5 (35.7)	12 (48)	0.34
Family history of CD [n(%)]	1 (7.1)	3 (1.2)	0.54
Family history of TD [n(%)]	7 (50)	10 (40)	0.39
Smoking [n(%)]	1 (7.1)	2 (8)	0.71
Pregnancies [n(%)]	2 (0-8)	2.5 (0-5)	0.51
Age (years)	52.7±15.1	49.7±11.7	0.49
Duration of CD (years)	5.0 (2.0–9.0)	6.0 (2.0–9.0)	0.73
Age of onset of CD (years)	46.4±18.3	44.0±10.4	0.66
BMI (kg/m^2)	23.9 ± 2.6	24.8±4.1	0.47
Duration of GFD (years)	4.0 (1.8–9.0)	5.00 (2.0–9.0)	0.63
Duration of TD treatment (years)	3.0 (0.0–8.0)	-	-
TSH (mIU/ml)	4.0 (2.1-5.1)	2.2 (1.6-2.7)	0.009
Anti-TPO (IU/ml)	24.2 (6.12-108.0)	7.13 (5-9.7)	0.013
FT4(ng/mL)	1.22 ± 0.33	1.12 ± 0.21	0.27

GFD: gluten-free diet; TD: thyroid dysfunction; BMI: body mass index; TSH: thyroid-stimulating hormone; TPO: thyroperoxidase; FT4: free thyroxine.
Data are shown as number (n) and percentage (%), mean±standard deviation, or median (P25/P75).

Table 3: Frequency of comorbid problems in patients with celiac disease (n=39).

Additional diseases	Number of patients	%
Anxiety symptoms	22	56.4
Iron deficiency anemia	20	51.3
Osteopenia or osteoporosis	19	48.7
Depression symptoms	15	38.5
Lactose intolerance	10	25.6
Hepatic dysfunction*	6	15.4
Anemia due to folic acid deficiency	5	12.8
Hepatitis C	5	12.8
Cancer	4	10.3
Alopecia	4	10.3
Dermatitis herpetiformis	3	7.7
Type 1 diabetes mellitus	2	5.1
IgA deficiency	1	2.6

*Chronic liver disease of unknown etiology was diagnosed in one patient. An increased level of transaminases of unknown origin was later detected in five patients.

DISCUSSION

Although frequently underdiagnosed, CD is a prevalent disorder. Today, the importance of detecting comorbidities in celiac subjects, such as autoimmune thyroid-related disorders, is well recognized. This has motivated researchers to seek more information on the prevalence of CD and its related comorbidities in different populations around the world. We found that hypothyroidism and subclinical hypothyroidism have a prevalence of 25.6%, and ATD has a prevalence of 35.9%, in a southern Brazilian sample of celiac patients in a tertiary care center.

A Brazilian study showed that thyroid diseases were the most common autoimmune diseases associated with CD (14). The risk of thyroid disease for celiac patients has been estimated to be almost 3 times higher than for the general population (14). In our study, subclinical hypothyroidism was detected in 5.1% of patients; clinical hypothyroidism in 20.5%, and positive anti-TPO antibodies in 15.4%. The prevalence of thyroid-related abnormalities was 35.9%. These results are in line with the literature. In a study conducted in Finland, positive anti-TPO antibodies were present in 11.4% of subjects with CD and in 5.1% of matched control subjects (10). As a result, Leeds et al. recommended yearly routine thyroid function tests (14). It is important to note that a GFD promotes better absorption of levothyroxine, which improves clinical control of hypothyroidism (14). On the other hand, Sategna et al. demonstrated that a long-term exposure to gluten in patients with CD did not increase the prevalence of autoimmune diseases (15). Moreover, a GFD does not prevent the development of autoimmune diseases (16). In another study involving patients diagnosed with late CD, the length of exposure to gluten in adult CD did not correlate with the risk of developing autoimmune disease, and gluten withdrawal did not protect patients from autoimmune disease (2).

The present study has some limitations: the prevalence of thyroid abnormalities in celiac patients was not compared to that in healthy subjects matched for age and sex, and all subjects were evaluated in a tertiary hospital. The convenience sample may also be insufficient, as it may not accurately represent the whole spectrum of CD in our population. Finally, our sample was small; a type II error in non-significant results cannot be ruled out.In summary, our study suggests that thyroid-related disorders are frequent in this population. It is recommended that celiac patients be screened for thyroid disease.

Our study reproduced previous findings on patients with CD. There is a high prevalence of thyroid-related abnormalities in celiac patients.

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Recebido: 08/04/2013
Aceito: 12/07/2013