

# Prevalence of thyroid eye disease in an Argentine tertiary hospital

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## Abstract

**Purpose:** Thyroid eye disease is the main extrathyroidal manifestation of Graves' disease. Regional or environmental factors may influence its manifestation; however, in Argentina its prevalence is unknown. The purpose of this study was to estimate the prevalence of thyroid eye disease and to review the clinical characteristics of Graves' disease patients from a tertiary hospital in Buenos Aires.

**Methods:** The charts of all patients diagnosed with Graves' disease between 2014 and 2016 were reviewed. Data of thyroid function tests, thyroid antibodies, clinical activity score, and severity grading were collected, and clinical characteristics of the patients with or without thyroid eye disease were compared.

**Results:** A total of 145 patients with Graves' disease were diagnosed. The prevalence of thyroid eye disease over two years was 22%. Only 9.3% of the patients with thyroid eye disease had moderate to severe disease. The average clinical activity score was  $1.1 \pm 1.3$ . There were no differences in thyroid-stimulating hormone, triiodothyronine, or anti-thyroid peroxidase levels between the thyroid eye disease and the non-thyroid eye disease group. Total and free thyroxine and the thyroid-stimulat-

ing hormone receptor antibody levels were significantly higher in patients with thyroid eye disease.

**Conclusion:** The prevalence of thyroid eye disease in patients diagnosed with Graves' disease from a tertiary hospital in Buenos Aires was 22%. The patients included in this study had a considerably milder presentation of thyroid eye disease than what has been reported in other regions.

**Keywords:** Graves' ophthalmopathy, orbital diseases, exophthalmos, diplopia, iodine, selenium.

## Prevalencia de enfermedad ocular tiroidea en un hospital argentino

### Resumen

**Objetivo:** La oftalmopatía distiroidea es la manifestación extra tiroidea más frecuente de la enfermedad de Graves. Los factores ambientales o regionales pueden condicionar su aparición, sin embargo se desconoce su prevalencia en la Argentina. El objetivo de este estudio fue estimar la prevalencia de oftalmopatía distiroidea y revisar las características clínicas de las personas con enfermedad de Graves en un hospital de Buenos Aires.

**Métodos:** Se revisó la historia clínica de todos los pacientes diagnosticados con la enfermedad de Graves entre los años 2014 y 2016. Se recolectaron datos serológicos y clínicos y se compararon las características clínicas de los pacientes con o sin oftalmopatía distiroidea.

**Resultados:** Se diagnosticó un total de 145 pacientes con enfermedad de Graves. La prevalencia en dos años de oftalmopatía distiroidea fue del 22%. Solo un 9,3% de los pacientes con oftalmopatía distiroidea tenía una enfermedad de moderada a grave. El puntaje de actividad clínica promedio fue  $1,1 \pm 1,3$ . No hubo diferencias en los valores de la hormona estimulante de tiroides, la triyodotironina o el anticuerpo de peroxidasa tiroidea entre el grupo de pacientes con o sin oftalmopatía distiroidea. Los valores de tiroxina total y libre y el anticuerpo antirreceptor de hormona estimulante de tiroides fueron significativamente mayores en pacientes con oftalmopatía distiroidea.

**Conclusión:** La prevalencia de oftalmopatía distiroidea en pacientes diagnosticados con enfermedad de Graves en un hospital de Buenos Aires fue

del 22%. Los pacientes incluidos en este estudio tuvieron un grado de enfermedad más leve que lo reportado en otras regiones.

**Palabras clave:** oftalmopatía de Graves, enfermedades orbitales, exoftalmia, yodo, selenio.

## Prevalência de doença ocular tiroideana em um hospital argentino

### Resumo

**Objetivo:** a oftalmopatia distiroideana é a manifestação extra tiroideana mais frequente da doença de Graves. Os fatores ambientais ou regionais podem condicionar sua aparição, no entanto, sua prevalência na Argentina é desconhecida. O objetivo deste estudo foi estimar a prevalência de oftalmopatia distireoidiana e revisar as características clínicas de pessoas com doença de Graves em um hospital de Buenos Aires.

**Métodos:** Foi revisado o histórico médico de todos os pacientes com diagnóstico de doença de Graves entre 2014 e 2016. Foram coletados dados sorológicos e clínicos e comparadas as características clínicas dos pacientes com ou sem oftalmopatia distireoidiana.

**Resultados:** Um total de 145 pacientes foram diagnosticados com doença de Graves. A prevalência de oftalmopatia distireoidiana em dois anos foi de 22%. Apenas 9,3% dos pacientes com oftalmopatia distireoidiana apresentavam doença moderada a grave. O escore médio de atividade clínica foi  $1,1 \pm 1,3$ . Não houve diferenças nos valores do hormônio estimulador da tireoide, triiodotironina (T3) ou anticorpo peroxidase tireoidiano entre o grupo de pacientes com ou sem oftalmopatia distireoidiana. Os valores de tiroxina total e livre e o de anticorpo e antireceptor do hormônio estimulante da tireoide foram significativamente maiores em pacientes com oftalmopatia distireoidiana.

**Conclusão:** A prevalência de oftalmopatia distireoidiana em pacientes com diagnóstico de doença de Graves em um hospital de Buenos Aires foi de 22%. Os pacientes incluídos neste estudo tinham um grau de doença mais brando do que o relatado em outras regiões.

**Palavras chave:** oftalmopatia de Graves, doenças orbitais, exoftalmia, iodo, selênio.

## Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism, with an annual incidence of 20-50 cases per 100,000 people<sup>1</sup>. It occurs most commonly in Caucasians and has a predilection for females, affecting 16 per 100,000 women and 3 per 100,000 men<sup>2</sup>. Although the disease can occur at any age, it peaks between the ages of 30 and 50<sup>2</sup>.

Thyroid eye disease (TED) is the most common extrathyroidal manifestation of GD. It occurs in up to 60% of patients with GD and can lead to a variety of clinical signs ranging from conjunctival hyperemia to sight loss due to dysthyroid optic neuropathy (DON)<sup>3-4</sup>.

The pathophysiology of TED involves an autoimmune reaction of T cells and mast cells against fat, muscle, and connective tissue within the orbit. This leads to swelling of muscle and fat, eventually causing some of the most common features of TED<sup>5</sup>. These include eyelid retraction (80%), proptosis (62%), and strabismus (43%)<sup>6</sup>. Among these features, DON is rare and only occurs in up to 3-8% of patients<sup>2,4</sup>.

Studies of monozygotic twins have revealed a concordance rate of 30-60% with regards to developing GD, indicating that a multifactorial interplay between genetics and the environment exist<sup>7</sup>. The strongest environmental correlates of moderate to severe TED appear to be smoking (conferring up to a 4-fold increase in risk) and selenium deficiency<sup>8-9</sup>. Other factors that have been studied include iodine levels (low and high)<sup>10</sup>.

Studies on the impact of the environment on TED are rare and difficult to perform due to the large number of confounding variables.

International variation in the incidence and morbidity of TED provides a potential avenue to address this gap in our knowledge. This study aimed to investigate the prevalence of TED and its clinical characteristics amongst patients with GD from a tertiary hospital in Buenos Aires.

## Methods

A cross-sectional study assessing the charts of all patients diagnosed with GD who presented at

the Hospital Italiano de Buenos Aires, between 2014 and 2016, was performed. The Hospital has an insurance service that provides healthcare to a population of 142,540. This group is predominantly Caucasian and of European descent (97%), while other ethnic minorities make up the remaining 3%.

The inclusion criteria were to be over the age of 18, to be a member of the Hospital's healthcare insurance, and to have a diagnosis of GD, defined by the presence of clinical or subclinical hyperthyroidism, with biochemical evidence of GD (low thyroid-stimulating hormone [TSH], normal or elevated triiodothyronine [T3] and thyroxine [T4], anti-thyroid peroxidase [TPO], and TSH receptor antibody [TRAb]).

The diagnosis of GD was confirmed by the endocrinology department. Serum levels of T3, total and free T4, TSH, TPO, and TRAb were measured. All patients with eye signs or symptoms were sent to the ophthalmology department for further assessment, where a decision was made on whether they had TED or not. In patients with TED, the following information was collected: clinical activity score (CAS), severity grading (EUGOGO classification), presence of strabismus or dysthyroid optic neuropathy (DON), and the amount of proptosis.

The first portion of the analysis involved comparison of parameters between TED and non-TED patients. The non-normally distributed age was compared using the Mann-Whitney U Test, while other parameters such as smoking, TSH, T3, T4 total, T4 free, TRAb, and TPO were compared using the Chi-squared test (X<sup>2</sup>). Statistical analysis was performed using SPSS version 22.0 (SPSS, Inc, Chicago, USA) and significance was defined as  $p < 0.05$ .

This study was conducted in accordance with the current regulations of the Helsinki Declaration and the protocol was approved by the Institutional Review Board.

## Results

A total of 146 patients were diagnosed with GD. One patient was excluded as he was diagnosed before 2014. Demographic details are pro-

**Table 1.** Characteristics of patients with and without TED.

	TED	Non-TED	p value
Gender			
Female, N (%)	27 (84%)	87 (77%)	0.368
Age (years), mean $\pm$ SD	47 $\pm$ 15.1	46 $\pm$ 17.0	0.478
Smoking, N (%)	9 (31%)	44 (12%)	0.019
TSH, mean $\pm$ SD	0.02 $\pm$ 0.05	0.04 $\pm$ 0.16	0.805
T3, mean $\pm$ SD	3.5 $\pm$ 2.5	2.6 $\pm$ 1.7	0.093
Total T4, mean $\pm$ SD	14.4 $\pm$ 5.4	12.2 $\pm$ 5.2	0.040
Free T4, mean $\pm$ SD	2.8 $\pm$ 1.6	2.2 $\pm$ 0.9	0.009
TRAb, mean $\pm$ SD	53 $\pm$ 26.1	32 $\pm$ 23.0	<0.001
TPO, mean $\pm$ SD	320 $\pm$ 493	559 $\pm$ 959	0.872

TED: thyroid eye disease. TSH: thyroid-stimulating hormone. T3: triiodothyronine. Total T4: total thyroxine. Free T4: free thyroxine. TRAb: TSH receptor antibody. TPO: anti-thyroid peroxidase.  $\pm$ SD: standard deviation.

vided in table 1. Of the patients diagnosed with GD, 114 were female with an average age of 48 standard deviation (SD)  $\pm$ 16.4 while 31 were male with an average age of 42.5 SD  $\pm$ 16.8. Of the 145 patients with GD, 32 were diagnosed with TED (2-year prevalence 22%). From this group, 27 were female (age 47.8, SD  $\pm$ 15.4) while 5 were male (age 42.8, SD  $\pm$ 14.5).

Clinically, 3 patients had moderate to severe disease (9.4%) while 29 (90.6%) had only mild disease. The average CAS for TED patients was 1.1 (SD 1.3). Only 3 (9.4%) had strabismus and none of the patients developed DON. The average proptosis value measured with Hertel exophthalmometer was 19.3 (SD  $\pm$ 2.8), though readings were missing for 8 patients (25%). The development of TED occurred after 21 weeks (SD  $\pm$ 33.8) following a diagnosis of hyperthyroidism. In 2 cases (6.2%), the diagnosis of TED was made prior to the diagnosis of GD.

No differences were found in TSH, T3, or TPO between the TED and the non-TED group. Total and free T4 and the TRAb values were significantly higher in patients with TED.

## Discussion

This study shows that over the course of two years, 145 patients were diagnosed with GD.

Only 22% of patients with GD eventually developed TED. This is much lower than previous reports that cite an association between GD and TED of up to 60%<sup>2,4</sup>. This study also found a much lower rate of moderate to severe TED. The frequency of diplopia was 2%, while there were no cases of DON. Previous studies had reported an incidence of 43% for diplopia<sup>6</sup>.

Only 2% of patients were graded as having moderate/severe disease (EUGOGO classification), while no patients had vision-threatening disease. The CAS was also low, with an average of 1.1 (SD  $\pm$ 1.3). The group of patients seen in this tertiary hospital had a decreased rate of developing TED from GD compared with oft-cited reports.

The patients included in this study were Caucasian and of European descent, however, they had a far milder form of TED than their counterparts living in Europe. Therefore, this

study provides a unique opportunity to review the potential environmental factors that might influence the manifestation of TED in Buenos Aires.

The TED group contained a greater number of smokers (31% vs 12%) and this agrees with numerous previous studies that support an association between smoking and TED<sup>11</sup>. Smoking is linked to a greater incidence and severity of TED. Our group has a similar number of smokers compared with previous studies<sup>12</sup>.

Iodine is another influential environmental factor. Argentina currently has a mandatory iodine supplementation program. Mild to moderate deficiency of iodine has been linked with the development of autoimmune thyroid disease (ATD). Pedersen *et al.* reported that the levels of TPO and anti-thyroglobulin were higher in the regions of Denmark that were mild and moderately deficient in iodine<sup>13</sup>. Laurberg *et al.* supported these findings in their study that found mild to moderate deficiency of iodine was related to the occurrence of ATD<sup>10</sup>. Furthermore, iodine supplementation programs in Switzerland have been associated with a decrease in thyrotoxicosis and Grave's disease<sup>14</sup>. These findings are supported by similar supplementation programs in Sri Lanka<sup>15</sup>.

The relationship between iodine levels and the development of ATD is complex. While the aforementioned studies support a role for the correction of iodine deficiency, others have suggested that over-supplementation may cause a transient rise in thyrotoxicosis<sup>16</sup>. Therefore, a "U" shaped curve may best describe this relationship, with both deficiency and excess contributing to thyrotoxicosis.

Selenium deficiency has been linked to autoimmune thyroid disease, and this is associated with the levels of selenium in the local soil and groundwater<sup>17-19</sup>. Recent geochemical work suggests that the areas around Buenos Aires have an increased level of iodine in the groundwater and sufficient levels of selenium<sup>20</sup>. This may prove to be a protective factor against moderate to severe TED.

The main limitation of this study is related to the population. This study is only reflective of

the patients that attended a tertiary hospital. This might mean that patients with moderate to severe TED may have attended other facilities. However, our hospital serves a population of 142,540 and to our knowledge, there is no accession bias for receiving care at our center.

Moreover, all the patients had an eye examination performed, but not all of them underwent an examination by an oculoplastic clinician.

This study represents a departure from the current narrative that suggests a high proportion of patients with GD develop TED and that a large group of these cases has diplopia. Our patients experienced a far milder presentation of TED than what has been suggested in other regions. Although this study has limitations from an epidemiological standpoint, the data raises the question as to whether iodine, selenium, or other environmental factors may be important in modulating the severity of TED.

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