Graves’ Ophthalmopathy: Epidemiology and Natural History

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Abstract

Graves’ ophthalmopathy (GO) is an autoimmune disorder of the orbit that is clinically relevant in 25-50% of patients with Graves’ disease and 2% of patients with chronic thyroiditis. The age-adjusted annual incidence of clinically relevant GO is 16 per 100,000 population in women and 2.9 in men. At the onset of ophthalmopathy, 80-90% of patients have hyperthyroidism, with the rest having euthyroidism or hypothyroidism. The natural history of GO consists of two phases: an active inflammatory phase and a static phase. Anti-inflammatory therapy is indicated for the first phase of GO. Approximately 5% of patients experience late reactivation of GO. Asians appear to have less severe manifestations, with milder orbital edema, proptosis and muscle restriction. Genetic, anatomic and environmental factors influence the development of GO. Aging, thyroid dysfunction, thyroid stimulating hormone (TSH) receptor antibodies, smoking and radioiodine treatment for hyperthyroidism also influence the development and course of GO.

Key words: Graves’ ophthalmopathy, Graves’ disease, epidemiology, prevalence, ethnicity

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Introduction

Graves’ ophthalmopathy (GO), also known as Graves’ orbitopathy, Graves’ eye disease, thyroid eye disease and thyroid-associated ophthalmopathy, is an autoimmune disorder of the orbit that is closely associated with autoimmune thyroid diseases. GO is clinically relevant in 25-50% of patients with Graves’ disease and 2% of patients with chronic thyroiditis (1-4). A subclinical form of GO can be detected on orbital imaging in more than 70% of patients with Graves’ disease. At the onset of ophthalmopathy, 80-90% of GO patients have hyperthyroidism, with the rest having euthyroidism or hypothyroidism. GO precedes the onset of hyperthyroidism in 20% of patients; however, it more frequently develops concomitantly or following the onset of hyperthyroidism. GO is usually bilateral, although it may be asymmetric or unilateral in 15% of patients. Sight is threatened in 3-5% of GO patients, with these patients requiring urgent treatment (1). There is considerable evidence that both genetic (5) and environmental (6) factors are involved in the development of GO. Although the primary autoantigen(s) and precise mechanisms underlying the association between GO and autoimmune thyroid diseases remain unclear, thyrotropin (TSH) receptors are thought to be the primary target of autoimmune reactions in GO patients.

In this review, we present the prevalence and natural history of GO, as well as risk factors that may influence its prevalence, including genetic factors, cigarette smoking and radiiodine treatment of hyperthyroidism. The definition of GO and the methods used to diagnose this condition also influence its estimated prevalence. Ethnic differences in the clinical presentation of GO are also described.

Epidemiology

Incidence of GO: The age-adjusted annual incidence of clinically relevant GO in a representative county in the United States (USA) was estimated to be 16 per 100,000 population in women and 2.9 per 100,000 in men, with an estimated prevalence of 0.25% (7). Subsequent studies in Europe (8-12), the USA (13, 14), India (15), Malaysia (16) and Japan (17) have reported prevalence rates ranging from...
0.1% to 0.3%, although one study from the USA reported a prevalence of 5.75% (14), likely due to environmental and/or anatomic factors.

**Thyroid function at the onset of GO:** The onset of GO in most patients is closely related to Graves’ hyperthyroidism. GO often develops concomitantly with hyperthyroidism, although it may precede or follow hyperthyroidism (18). In a study from Pisa, Italy, GO was found to be associated with hyperthyroidism in 202 of 221 (91.4%) patients (19). In another cohort study, 90% of the GO patients had hyperthyroidism, 3.3% had Hashimoto’s thyroiditis and 5.8% were euthyroid (20). GO and hyperthyroidism occur within 18 months of each other in 60% to 85% of patients (19, 21-23). GO can occur in patients who develop hyperthyroidism at a later age or may develop some time after the treatment of hyperthyroidism (22-24).

The overall incidence of GO in patients who have never been hyperthyroid (euthyroid Graves’ disease and hypothyroid Graves’ disease) varies from 2.5% to 34.3% (20, 25-28), with differences being due to referral biases or other factors. Up to 50% of initially euthyroid patients develop hyperthyroidism within 18 months (23).

**Clinical presentation**

The clinical presentation of GO varies by age, gender and race. Several differences in clinical presentation have been observed between Asian and Caucasian patients.

**Age and sex distribution:** GO patients are older than patients with GD without ophthalmopathy (mean age: 46.4 years vs. 40.0 years) (28). Bimodal peaks in age onset have been observed in both men and women, with both peaks occurring five years earlier in women than in men (40-44 years vs. 45-49 years and 60-64 years vs. 65-69 years) (7). In an observational case series of 10,931 consecutive Japanese patients with GO treated at one clinic from 1993 to 2002, the mean age at GO onset was 39.1 years in women and 43.0 years in men (29).

Most patients with GO exhibit both enlargement of extraocular muscle and expansion of adipose tissue, with some showing a predominance of one feature or the other. Patients under 40 years of age tend to demonstrate fat expansion, whereas patients over 60 years of age display more extraocular muscle swelling (2, 30).

GO is more common in women than in men. The female to male ratio is 4.2 in Swedish patients (31) and 3.9 in Japanese subjects (29). Moreover, the female to male ratio varies according to the severity of ophthalmopathy, being 9.3, 3.2 and 1.4 in patients with mild, moderate and severe ophthalmopathy, respectively (28). Another study reported female to male ratios of 3.4 and 2.1 among patients with hyperthyroid Graves’ disease without and with ophthalmopathy, respectively, and 0.7 among patients with euthyroid Graves’ disease (19). In a recent cohort of 2,045 patients with Graves’ disease, the rates of NOSPECS classes IV-VI were 30.4% in men and 21.3% in women (32). Taken together, these studies indicate that GO tends to be more severe in older patients than in younger patients and in men compared to women. The higher prevalence of smoking in men, as well as gender-related genetic factors, may play a role in the severity of GO.

**GO in children:** GO is rare in children, occurring in 0.1 per 100,000 prepubescent and 3.0 per 100,000 postpubescent children (33). No ethnic differences have been reported in children or adolescents. The clinical manifestations of GO are less severe in children and adolescents than in adults (Table) (34). Soft tissue involvement and proptosis were the predominant eye changes in 77 GO patients described in five studies (35-39). More severely restricted eye muscle movement and optic dysfunction almost never occur in children. The prevalence of GO in children and teenagers is related to the prevalence of smoking among teenagers in various countries (34).

**Anatomical differences between races:** Racial differences in ocular anatomy in normal subjects and GO patients have been extensively reviewed (40, 41). Normal exophthalmometry values vary significantly among races, with Asians having low values and blacks having relatively shallow orbits and higher values (42-45). Furthermore, there are differences in the eyelid and orbital septum between Caucasians and Asians. Apical compression and optic neuropathy occur more frequently in Asians due to their shallower orbits and narrower apices (41, 46).

**Clinical features:** GO is clinically relevant in 25% of unselected patients with Graves’ disease if eyelid signs are excluded and 40% if eyelid signs are included (47). Orbital imaging, such as magnetic resonance imaging (MRI) and

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**Table. Clinical Presentation of Eye Changes in Patients with Graves’ Ophthalmopathy**

<table>
<thead>
<tr>
<th></th>
<th>Dickinson(1)</th>
<th>Krassas(4)</th>
<th>Kozaki(29)</th>
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</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Japanese</td>
<td></td>
</tr>
<tr>
<td>GO patients</td>
<td>77 GO patients</td>
<td>10921 GO patients</td>
<td></td>
</tr>
<tr>
<td>Lid retraction</td>
<td>90-98%</td>
<td>57.0%</td>
<td></td>
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<tr>
<td>Lid swelling</td>
<td>75%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Proptosis</td>
<td>63%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Extraocular muscle involvement</td>
<td>40-60%</td>
<td>6.5%</td>
<td>40.8%</td>
</tr>
<tr>
<td>Corneal involvement</td>
<td>10-17%</td>
<td>30%</td>
<td></td>
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<tr>
<td>Optic nerve involvement</td>
<td>5%</td>
<td>0%</td>
<td>7.3%</td>
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GO: Graves’ ophthalmopathy
computed tomography (CT) show enlargement of the extraocular muscles, an increase in the orbital fat tissue volume and enlargement of the lacrimal glands (48, 49) (Fig. 1A, C). In addition, orbital imaging reveals abnormalities in almost all patients with GO. The clinical activity score (CAS) is useful for assessing the GO activity. If the CAS is more than 3, immunosuppressive therapy is recommended for the treatment of GO in Europe (50). The CAS values, however, tend to be low in Japanese GO patients who are receiving intravenous steroid pulse therapy (51). The NOSPECS classification remains a useful reminder of the features that should be assessed (52, 53).

Class 0: More than half of patients with Graves’ disease do not have evident ophthalmopathy. However, approximately 70% of patients with untreated Graves’ disease without signs or symptoms of ophthalmopathy exhibit an enlargement of the extraocular muscles, a condition termed ‘occult thyroid eye disease’ (54-56). Imaging modalities, such as CT and MRI, are useful for evaluating these conditions.

Class I (Only signs): Upper lid retraction, staring and eyelid lag are observed in 35-53% of patients with Graves’ disease (16) and in 90-98% of Caucasian patients (19, 20) and 57% of Japanese patients (29) with GO.

Class II (Soft tissue involvement): Class II signs are common, affecting 32% of patients with Graves’ disease (47). Lid swelling is observed in 47% of GO patients, with injection and edema of the conjunctiva observed in 32% (29).

Class III (Proptosis): Proptosis is observed in 24% of untreated patients with Graves’ disease and 63-74% of patients with GO (29, 47).

Class IV (Extraocular eye muscle involvement): Approximately 22% of patients suffer from diplopia. Enlargement of the extraocular muscles is observed in 41% of GO patients (29). The enlarged eye muscle is no longer able to lengthen and causes diplopia (Fig. 1D). In most patients with this class of disease, several extraocular muscles are affected to various degrees. Therefore, MRI is useful for evaluating orbital lesions in patients with GO. A high signal intensity on STIR images may indicate inflamed extraocular muscles (48) (Fig. 1B).

Class V (Corneal involvement): Although punctuate staining is observed in 10-17% of patients, the incidence of sight-threatening ulceration was <2% a century ago and it is probably lower now (1).

Class VI (Sight loss): Optic nerve involvement, so-called dysthyroid optic neuropathy, is observed in 3-7% of GO patients (1, 29).

Caucasians have been reported to be at greater risk of developing GO than Asians (42% vs. 7.7%) (57). Moreover, Asians appear to have less severe manifestations, with milder features of orbital edema, proptosis and muscle restriction (46). A cross sectional study of Malay, Chinese and Indian GO patients with Graves’ disease in Malaysia showed that the prevalence of GO ranged from 35.1% to 40.0% in the three populations, similar to the prevalence observed in Caucasians (16). A similar frequency of GO of 33% has been documented in juvenile patients with Graves’
disease (58). The incidence of GO in Japanese is similar to that observed in Caucasians (Table). Taken together, these studies show that, although the prevalence of GO may not differ among ethnic groups, the clinical features of GO differ, being milder in Asians than in Caucasians.

A study conducted in Sweden based on the registry of a Swedish Multicenter Study found that 20% of patients with GD had orbitopathy, with 4.9% having infiltrative signs and/or symptoms and 15.2% having non-infiltrative symptoms (31). In that study, there were geographic differences in the incidence of GD. The study also found that smoking did not significantly influence the incidence of GO.

A prospective, population-based study conducted in Denmark found that approximately 5% of patients with Graves’ disease develop moderate to severe GO, with similar risks observed in women and men. The risk of GO is much higher in patients 40–60 years of age than in younger patients with Graves’ disease (59).

In one clinic in the United Kingdom (60) the prevalence of GO fell from 57% in 1960 to 37% in 1990, a decrease that may be related to the decrease in smoking in Western countries during this period of time. In contrast, the prevalence of GO increased in Poland and Hungary where the prevalence of smoking also increased (61). Other factors, such as a greater awareness of GO in Graves’ disease patients as well as improved laboratory testing of the thyroid function may also have contributed to the decline in prevalence in individual clinics (47).

Natural history

The natural history of GO was first described by Rundle (62, 63). Progressive deterioration may occur over 6–24 months, due to the development of the autoimmune process (dynamic active progressive phase, Fig. 2A). This stage is characterized by lymphocyte infiltration, with the cells secreting various cytokines, along with fibroblast proliferation and edema. As the inflammatory activity subsides, a plateau is reached, followed by a phase of spontaneous slow improvement that may last a year or more. Regression of the inflammatory process may lead to fibrosis, preventing affected tissues from returning to their previous healthy state (static phase). Anti-inflammatory therapy is indicated in the first phase and corrective surgery may be indicated in the second phase (Fig. 2B-D) (64).

A long-term follow-up study showed that the general appearance of the patients had improved after 15 years, although approximately 50% still had obvious signs of orbitopathy (63).

In a study of 122 patients with thyrotoxicosis, exophthalmos remained stable in 78.7% of the patients, improved in 5.7% of the patients and worsened in 15.6% of the patients (65). In a small series of 59 patients with mild GO referred to a combined thyroid eye clinic and assessed every three months for one year or more, 13 (22%) experienced substantial improvement, 25 (42%) experienced a slight improvement, 13 (22%) exhibited unchanged ocular involvement and eight (14%) demonstrated progression to a more

Figure 2. Natural history of Graves’ ophthalmopathy (GO) depicting the severity of GO over time (Rundle’s curve) (A). The administration of immunosuppressive treatment during the early active phase of GO results in a reduction of both the disease activity and severity (B). The administration of immunosuppressive treatment during the late inactive phase of GO does not result in any benefits for the course of GO (C). During the late inactive phase, rehabilitative surgery results in great benefits (D). (Modified from ref. 64 with permission)
severe form of GO (66). In contrast, a study involving 81 patients followed-up for 2.7 years found that 25 of 53 (47%) patients showed improvements in ophthalmopathy with no therapy or only local protective agents, 26 (49%) showed no changes and two (4%) showed deterioration (67). In a more recent cohort study of 346 patients with newly diagnosed and recent onset Graves’ hyperthyroidism, 255 (73.7%) had no ocular involvement, 70 (20.2%) had mild and inactive GO, 20 (5.8%) had moderate-to-severe and active GO and one (0.3%) had sight-threatening GO with dysthyroid optic neuropathy (68). Progression from moderate to severe GO occurred in 2.6% of patients without orbitopathy and in 2.3% of those with mild GO at baseline (68). These findings indicate that a spontaneous improvement occurs in approximately 30% of patients with mild to moderate GO.

Several studies have suggested that prompt restoration and stable maintenance of euthyroidism is important for the natural history of GO. Anti-thyroid drugs (ATDs) and thyroidectomy do not influence the natural history of GO. Radioiodine therapy can induce the progression or de novo development of GO, particularly in smokers (69, 70). This effect can be prevented by the administration of oral steroid prophylaxis. Two cohort studies in which the patients received levothyroxine therapy soon after radioactive iodine with the specific intent of preventing hypothyroidism found that deterioration of GO was rare (0-2%) (71, 72). A randomized trial of patients newly diagnosed with Graves’ disease found that radioactive iodine did not increase the risk of worsening GO compared with methimazole [relative risk (RR), 0.95], when the development of hypothyroidism was therefore prevented by the administration of oral steroid two weeks after radioactive iodine treatment (RAI) (73).

In patients with mild orbitopathy, the choice of thyroid treatment is largely independent of GO. A series of 72 patients with inactive GO according to the CAS were treated with radioactive iodine without concurrent glucocorticoid administration (69). GO activation was observed in approximately 7% of the patients considered to be at low risk and therefore given no steroid prophylaxis. Whether concomitant treatment of hyperthyroidism in these patients should be conservative (ATDs) or ablative (RAI and/or thyroidectomy) is presently based on expert opinion rather than evidence. The American Thyroid Association and American Association of Clinical Endocrinologists have provided guidelines to assist health care professionals in making medical decisions for specific clinical conditions in patients with GO (74).

Late reactivation of GO, defined as active orbitopathy occurring after more than five years of quiescent disease, appears to be uncommon, being reported in only 5% of GO patients (75).

**Risk factors**

Several risk factors may influence the occurrence of GO. These include genetic factors, smoking, the presence of TSH receptor antibodies [TSH binding inhibitor immunoglobulins (TBIIs) >50% or thyroid stimulating immunoglobulin (TSI) >8.8 IU/L] (76), a high pretreatment T3 concentration (≥235 ng/dL or ≥2 nmol/L) (69), an advanced age, stress, drugs, iodine intake, ¹³¹I therapy (66) and hypothyroidism following radioiodine treatment (68).

**Genetic factors**: GO is generally regarded to be an autoimmune disease and genes related to its immuneopathogenesis in the orbit may be involved in susceptibility to GO (5). The human leukocyte antigen (HLA)-DRB1*03, DRB1*04 and DRB1*07 genotypes have been shown to be related to the development of GO in Caucasians. In Asian populations, the association between HLA and GO is less clear. Polymorphisms in immunomodulatory genes have been reported to be associated with GO, including genes encoding cytokotic T lymphocyte antigen (CTLA-4), interleukin-1 (IL-1) and members of the IL-1 family, interferon (IFN)γ, IL-23R, CD40, protein tyrosine phosphatase, non-receptor type 22 (PTPN22), nuclear factor-kappa B (NF-kB) and tumor necrosis factor α (TNFα) (77), as well as thyroid specific genes (TSH receptor gene) and adipogenesis-related genes, such as peroxisome proliferator-activated receptor γ (PPARγ). These findings are based on small case-controlled association studies and suggest racial differences in genetic associations (41). These results, however, require confirmation in large-scale studies.

**Cigarette smoking**: Cigarette smoking is the strongest modifiable risk factor for the development of GO. A meta-analysis (78) of case control studies as well as cohort studies (71, 72) demonstrated strong links between tobacco smoking and the development and deterioration of GO. One study reported that 64% of patients with GO and 48% of Graves’ disease patients without orbitopathy were smokers, compared with approximately 30% of patients with nontoxic goiters, toxic goiters or Hashimoto’s thyroiditis (79). Smoking causes GO progression following radiotherapy for Graves’ disease and attenuates the efficacy of orbital radiotherapy and high-dose systemic glucocorticoids (80). The pathogenic mechanisms underlying the effects of smoking on GO are not fully understood.

**Anti-TSH receptor antibodies**: Since TSH receptor mRNA and proteins are present in orbital adipose tissue and an increased expression of this receptor has been reported in the orbital adipose tissue of patients with GO (2), autoimmunity against the TSH receptor may play a major role in the development of GO. The TBI titers and TSI concentrations have been reported to be associated with GO development (81-84), and TSI has been found to be directly associated with the CAS and response to anti-inflammatory therapy (85-87).

**¹³¹I therapy for hyperthyroidism**: The development or worsening of GO after radioiodine therapy for hyperthyroidism has been reported in 15-39% of patients (69, 70, 73). Randomized controlled trials found that the risks of radioiodine were greater than those for anti-thyroid drugs, e.g., 15% vs. 3% (67), 33% vs. 10% (69) and 38.7% vs. 21.3% (73), respectively. Radioiodine therapy is also associ-
ated with a greater risk of ophthalmopathy than anti-thyroid drugs [RR, 4.23; 95% confidence interval (CI), 2.04-8.77] (88). Glucocorticoid prophylaxis is beneficial for patients with mild pre-existing GO (70). A transient increase in the level of TSH receptor antibodies has been reported after radioiodine therapy (89). Therefore, radioiodine therapy may trigger the development of autoimmune inflammation in the orbit and result in the worsening of GO. The ability to prevent the deterioration of GO with the early administration of T4 suggests that the development of hypothyroidism after radioiodine therapy may be a more important risk factor for the development of GO (71, 72).

**Conclusion**

GO is an autoimmune disease of the orbit that is frequently associated with Graves’ disease. The age-adjusted annual incidence of clinically relevant GO in a representative county is estimated to be 16 per 100,000 population in women and 2.9 per 100,000 in men. The estimated prevalence of clinically relevant GO ranges from 0.1% to 0.3%. At the onset of orbitopathy, 80-90% of GO patients have hyperthyroidism, with the rest having either euthyroidism or hypothyroidism. Approximately 5% of patients exhibit late reactivation of GO.

Lid retraction is observed in 57-98% of adults with GO, with proptosis in 63-74%, extraocular muscle involvement in 40-60% and optic neuropathy in 5-7%. However, a subclinical form of GO is demonstrated on orbital imaging in more than 70% of patients with Graves’ disease.

The natural history of GO consists of two phases: an active inflammatory phase and a static phase. The rate of development or progression to a more severe form of GO is 4% to 15%. Anti-inflammatory therapy is indicated in moderate to severe GO patients in the first phase.

Several racial and/or geographic differences are observed in the clinical presentation of GO. Genetic, anatomic and environmental factors are involved in the development of GO. Aging, thyroid dysfunction, TSH receptor antibodies, cigarette smoking and radioiodine treatment for hyperthyroidism also influence the development and course of GO.

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**References**


67. Noth D, Gebauer M, Müller B, Bürgi U, Diem P. Graves’ ophthalm-


