

## MINI REVIEW

**Graves' ophthalmopathy: a preventable disease?**Luigi Bartalena, Claudio Marcocci<sup>1</sup> and Aldo Pinchera<sup>1</sup>*Cattedra di Endocrinologia, University of Insubria, Varese and <sup>1</sup>Dipartimento di Endocrinologia, University of Pisa, Pisa, Italy**(Correspondence should be addressed to Luigi Bartalena, University of Insubria, Ospedale di Circolo, Viale Borri 57, 21100 Varese, Italy; Email: l.bartalena@libero.it)***Abstract**

Most patients with Graves' disease have some degree of ocular involvement, but only 3–5% of them develop severe ophthalmopathy (1). The reasons why only such a minority of patients with Graves' disease have severe expression of the ophthalmopathy remain to be elucidated. One possible explanation is that non-severe ophthalmopathy and severe ophthalmopathy are two different disorders with different genetic backgrounds; alternatively, they might be part of a spectrum of different conditions ranging from absent ocular involvement to most severe ophthalmopathy. In this case, external variables (i.e. environmental factors) must contribute to the nature of the expression of the disease. How important are they? How far can our intervention on environmental factors go towards reducing the risk of progression of the ophthalmopathy? In other words, to which extent, if any, is Graves' ophthalmopathy preventable? The aim of this mini-review is to address the above issues.

*European Journal of Endocrinology 146 457–461***Risk factors**

Risk factors for the occurrence or progression of Graves' ophthalmopathy have been partially identified (Table 1), but the list is probably much longer, and efforts of future research should be aimed at identifying most of them. Some of the identified risk factors can be prevented, but others can not.

**Non-preventable risk factors**

**Genetic factors** The genetics of Graves' ophthalmopathy is poorly understood. Graves' disease appears to be a multifactorial disease, resulting from both inborn genetic susceptibility and environmental triggering factor(s) (2). Genetic susceptibility has been evaluated by assessing human leucocyte antigen (HLA) system associations. However, although some studies showed an association of the ophthalmopathy with HLAs-DR3 and -B8, other studies were unable to confirm these results (3). A recent segregation analysis of patients with severe ophthalmopathy failed to demonstrate hereditary transmission of eye disease, even in families who manifested a strong genetic influence on the development of Graves' disease (4). Thus it seems likely that environmental factors have a more important role than do genetic factors in the development of Graves' ophthalmopathy. Nevertheless, some genetic contribution to the risk of occurrence of the ophthalmopathy probably exists, but this remains to be defined.

**Age** Although Graves' ophthalmopathy may occur in all age groups, a recent study from Olmsted County, Minnesota showed that the age-specific incidence of Graves' ophthalmopathy is bimodal in both women and men, with two peaks – in the 40–44-year-old and 60–64-year-old age groups in women, and some 5 years later in men (5). Concomitant risk factors should particularly be sought for in these high-risk age groups.

The risk of developing Graves' ophthalmopathy thus appears to increase with age. This concept is in keeping with the notion that Graves' ophthalmopathy is rare, at least in its severe manifestations, in juvenile Graves' disease (6).

**Sex** The influence of sex on the occurrence and progression of Graves' ophthalmopathy has been evaluated in several studies. Among them, Marcocci *et al.* (7) observed that the female:male ratio of patients was 3.4 for those with Graves' disease without apparent ocular involvement, but it decreased to 2.1 in patients with the ophthalmopathy, and to 0.7 in patients with euthyroid Graves' disease. Sex seems also to influence the severity of Graves' ophthalmopathy. Perros *et al.* (8) found female:male ratios of 9.3 in patients with non-severe ophthalmopathy, 3.2 in patients with ophthalmopathy of moderate degree, and 1.4 in patients with severe ophthalmopathy. Thus men tend to have a relatively increased prevalence of Graves'

**Table 1** Risk factors for occurrence/progression of Graves' ophthalmopathy.

Factor	Notes
<b>Non-preventable</b>	
Genetic	Poorly defined
Age	Incidence peaks in the 5th and 7th decades
Sex	More severe disease in (older) men
<b>Preventable</b>	
Cigarette smoking	Association of smoking with Graves' ophthalmopathy, its severity and reduced response to treatment
Thyroid dysfunction	Both hyper- and hypothyroidism may negatively affect the outcome of the ophthalmopathy
Radioiodine treatment	Progression of eye disease occurs in 15% of patients after radioiodine treatment

ophthalmopathy and more severe disease than women. The reasons for these sex-related differences are not clear, but external variables, such as the disproportionately greater prevalence of smokers among men, are probably involved (see below).

### Preventable risk factors

**Cigarette smoking** After the initial report by Hagg & Asplund (9), several reports have documented a close association between cigarette smoking and Graves' ophthalmopathy (see 10 for review). In a cross-sectional study of the smoking habits of 1730 women, we reported a prevalence of smokers of 48% among patients with Graves' disease but without apparent ocular involvement, and 64% among those with associated ophthalmopathy (11). These figures were significantly greater than the prevalence of 30% found in the control groups with other autoimmune and non-autoimmune thyroid disorders (11). Prummel & Wiersinga (12), in a consecutive-entry case-control study, observed that cigarette smoking greatly increased the risk of developing the ophthalmopathy. Furthermore, among patients with Graves' ophthalmopathy, smokers tended to have more severe ocular involvement than non-smokers, although there was no significant association between the degree of tobacco consumption and severity of the ophthalmopathy (12). In a recent prospective study of 253 patients with Graves' disease, cigarette smoking was associated with a 1.3-fold increase in the risk of developing clinical ophthalmopathy, and with 2.6-fold and 3.1-fold increases in risk of developing proptosis and diplopia respectively (13). Interestingly, these risks were associated with current smoking rather than with life-time tobacco consumption, and former smokers had a lower risk of developing ophthalmopathy than current smokers with a comparable total tobacco consumption (13). Whether the latter observation implies that refraining from smoking may improve the course of established ophthalmopathy or decrease the risk of *de novo* occurrence of eye disease remains to be confirmed by appropriate prospective and randomized studies. In addition, cigarette smoking has been documented to have a negative influence on the

effectiveness of orbital radiotherapy and high-dose systemic glucocorticoids: in one recent study the proportion of responders to treatment was significantly different in smokers and non-smokers (58 of 85 smokers (68%) and 61 of 65 non-smokers (94%) responding) (14). The mechanisms whereby cigarette smoking affects the ophthalmopathy remain to be clarified. In addition to direct irritant effects, smoking may affect the immune reactions involved in the pathogenesis of Graves' ophthalmopathy (10). In particular, smoking might enhance cytokine secretion and activity by causing hypoxia in the retrobulbar space (15). In summary, cigarette smoking appears to be a definite (and removable) risk factor for the occurrence of Graves' ophthalmopathy and for a less successful outcome of its medical treatment.

**Thyroid dysfunction** Graves' ophthalmopathy is most often associated with hyperthyroidism caused by Graves' disease, although in a minority of cases it may occur in patients with no present or past history of hyperthyroidism (euthyroid Graves' disease) or in patients with hypothyroid Hashimoto's thyroiditis (7). What is the relationship between the abnormal thyroid status and the outcome of ophthalmopathy? Hyperthyroidism seems to influence the clinical course of eye disease. In a study of 87 patients with Graves' disease followed for more than 5 months, no substantial changes in ocular condition were observed among the 54 patients who were euthyroid at the time of first observation; conversely, among the 33 patients who were hyperthyroid when first seen, eye disease progressively improved with time after restoration of euthyroidism, as assessed by the decrease in the total eye score (16). In a consecutive-entry study, 287 patients with Graves' disease were subdivided into four groups (A to D) according to increasing severity of ocular involvement and the proportion of hyperthyroid patients was found to be greater in patients with more severe ophthalmopathy (group C, 61%; group D, 47%) than in those with milder expressions of the disease (group A, 23%; group B, 32%) (17).

The findings of both the above studies suggested that careful control of hyperthyroidism may be associated with a more favourable outcome of the ophthalmopathy.

This assumption seems to be supported by a study of 264 patients treated with radioiodine and followed for 10 years thereafter: progression of the ophthalmopathy was more frequently observed among patients who required more than one dose of radioiodine to achieve permanent control of hyperthyroidism (15 of 127; 12%) than among patients who became hypothyroid after the first radioiodine treatment (two of 48; 4%) (18). In contrast, in a study of 30 patients with severe ophthalmopathy, the onset of eye disease occurred in nine after radioiodine treatment, in three after temporary withdrawal of thionamide, but in 15 after a period of varying duration of hypothyroidism associated with increased serum thyroid-stimulating hormone (TSH) concentrations (19). In other words, not only hyperthyroidism, but also hypothyroidism may negatively influence the course of the ophthalmopathy. Thus prompt correction of either spontaneous or treatment-induced hypothyroidism appears to be essential for avoiding progression of eye disease. The mechanism whereby thyroid dysfunction is linked with a progression of eye disease is probably related to TSH receptor activation (by TSH-receptor antibody in hyperthyroidism, by TSH in hypothyroidism), leading to increased expression, release, or both, of thyroid antigens and to subsequent enhancement of autoimmune reactions directed towards antigens shared by the thyroid and the orbit (1).

**Radioiodine treatment** It is widely accepted that antithyroid drug treatment (20) and near-total thyroidectomy (21) do not affect the course of the ophthalmopathy, but radioiodine treatment carries a small but definite risk of causing progression of eye disease (22). Few randomized and controlled studies are available on this subject. In a pilot study, hyperthyroid patients with Graves' disease were randomly assigned either to treatment with radioiodine alone or to treatment with radioiodine associated with prednisone treatment. Progression of the ophthalmopathy occurred in nine of the 26 patients (35%) receiving radioiodine treatment alone, but in none of those concomitantly treated with glucocorticoids (23); indeed, in most of the latter patients, pre-existing ophthalmopathy improved (23). In a subsequent large, randomized and controlled study, Tallstedt *et al.* (24) found that the rate of occurrence or aggravation of the ophthalmopathy was much greater after radioiodine treatment (13 of 39 patients;

33%) than after thionamide treatment (four of 38 patients; 10%) or thyroid surgery (six of 37 patients; 16%). Finally, in a prospective, randomized and controlled study, we found that 23 of the 150 patients receiving radioiodine treatment manifested a progression of the ophthalmopathy, which was transient in 15, but permanent in eight patients, who then required treatment for eye disease (20). As in our previous study, this exacerbation of the ophthalmopathy did not take place if patients were concomitantly treated with glucocorticoids.

The view that radioiodine treatment may be responsible for the progression of the ophthalmopathy is not shared by all authors (25), mostly on the basis of results of retrospective and uncontrolled studies (26).

The risk of radioiodine-associated exacerbation of the ophthalmopathy is increased if the patient smokes or has high pretreatment serum thyroid hormone, TSH-receptor antibody or TSH concentrations (1). Late correction of post-radioiodine hypothyroidism also seems to increase this risk. Progression of eye disease after radioiodine treatment is probably related to the exacerbation of autoimmune reactions to antigen(s) shared by the thyroid and orbit and released from the thyroid as a consequence of radiation-induced thyroid damage (1).

### Guidelines for minimizing the risk of progression of the ophthalmopathy

On the basis of the above discussion, it is clear that currently there is no means of intervening with respect to genetic factors possibly involved in the pathogenesis of Graves' ophthalmopathy. Likewise, with respect to the advanced age of the patient or male sex that can be regarded as possible risk factors for the occurrence of the ophthalmopathy, particularly of severe forms, there is no means of active preventive intervention, except, perhaps, for a closer surveillance of such patients. Conversely, there is room for action on preventable risk factors (Table 2). *Early diagnosis and treatment of hyperthyroidism* are probably of importance in improving the outcome of the ophthalmopathy. This is the likely explanation for the finding that the number of patients with Graves' disease who are affected with the ophthalmopathy and the severity of eye disease have apparently been declining in the recent decades (27). A contribution to this improved

**Table 2** Actions on preventable risk factors for Graves' ophthalmopathy.

Risk factor	Action
Cigarette smoking	Smoking cessation
Hyperthyroidism	Restoration of euthyroidism by antithyroid treatment
Recurrent hyperthyroidism	Ablative treatment
Hypothyroidism	Restoration of euthyroidism by L-thyroxine
Radioiodine treatment	Glucocorticoid coverage after radioiodine treatment

outcome probably derives also from *earlier diagnosis and treatment of the ophthalmopathy* itself: it is obviously much easier (at least for medical treatment) to intervene successfully in eye disease of recent onset than in long-standing ophthalmopathy, characterized by irreversible, fibrotic changes (28).

Another important measure is represented by *correction of hyperthyroidism*. As discussed above, the course of eye disease appears to be better in patients whose hyperthyroidism is corrected (16). In this regard, it is worth noting that *avoidance of recurrences of hyperthyroidism* may be crucial for the ophthalmopathy, because the continuing thyroid activity (and the associated autoimmune reactions) may be detrimental to the ophthalmopathy. Antithyroid drug treatment is an effective treatment for hyperthyroidism, but its major drawback is represented by the high rate of relapse (29). Accordingly, it is our opinion, not shared by all authors (22, 30), that, in patients with Graves' ophthalmopathy, definitive treatment of hyperthyroidism is to be preferred (31). Surgical treatment is a valid option, even in patients in whom the goitre is not large, in view of the absence of effects on eye disease. It remains to be clarified whether total thyroid ablation by thyroidectomy followed by radioiodine treatment may represent, as suggested by the findings of an uncontrolled study by DeGroot & Benjasuratwong (32), the best definitive treatment of hyperthyroidism with respect to the outcome of the ophthalmopathy. The fact that *radioiodine treatment* may cause a progression of the ophthalmopathy should not, however, be considered as an argument to avoid this treatment in patients with clinical eye disease. The results of a survey among European thyroidologists showed that the majority of respondents chose surgery rather than radioiodine treatment, when definitive treatment was selected (33). However, even in high-risk patients, progression of eye disease does not occur if, as mentioned above, radioiodine treatment is administered together with glucocorticoid 'protection' (34).

If hyperthyroidism may be detrimental to the ophthalmopathy, *correction of hypothyroidism* also may be important for minimizing the risk of progression of eye disease. Interestingly, progression of the ophthalmopathy after radioiodine treatment is much less common if hypothyroidism is corrected promptly than if initiation of L-thyroxine replacement is delayed, leaving the patient hypothyroid for a variable period of time (35).

Among other risk factors, *cessation of smoking* is certainly the most important intervention. Although data on the effects of refraining from smoking are scant, the evidence on the role of smoking in terms of worsening the course of the ophthalmopathy and decreasing its response to treatment is so strong that all patients with Graves' disease should be urged to stop smoking, irrespective of the presence or absence of ophthalmopathy at the time of first observation. In a recent

editorial, Keltner (36) stated that he is so convinced of the major role of cigarette smoking that he tells his patients with Graves' ophthalmopathy that they will not be operated on for strabismus surgery unless they refrain from smoking for at least 1 month before surgery. Because patients with Graves' ophthalmopathy are highly motivated and ready to do everything they can to alleviate a disease that profoundly affects the quality of their life (37), it is possible that, at least in a substantial proportion of patients, this can lead to valuable results.

## Concluding remarks

Graves' ophthalmopathy, a multifactorial disorder to which both endogenous (genetic factors, age, sex) and exogenous (cigarette smoking, thyroid dysfunction, radioiodine treatment) factors contribute, is only partially preventable. Partial prevention can be achieved by intervening with respect to environmental factors, which currently seem to be more important than non-preventable endogenous factors. This leaves the possibility that a correct and careful diagnostic and therapeutic approach to both hyperthyroidism and the ophthalmopathy, together with behavioural changes (cessation of smoking), may lead to an improved prognosis of this incapacitating and disfiguring disease.

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## References

- 1 Bartalena L, Pinchera A & Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. *Endocrine Reviews* 2000 **21** 168–199.
- 2 Tomer Y & Davies TF. The genetic susceptibility to Graves' disease. *Bailliere's Clinical Endocrinology and Metabolism* 1997 **11** 431–450.
- 3 Tomer Y & Davies TF. The genetics of familial and non-familial hyperthyroid Graves' disease. In *Graves' Disease – Pathogenesis and Treatment*, pp 19–41. Eds B Rapoport & SM McLachlan. Boston: Kluwer Academic Publisher, 2000.
- 4 Villanueva R, Inzerillo AM, Tomer Y, Barbesino G, Meltzer M, Concepcion ES, Greenberg DA, MacLaren N, Sun ZS, Zhang DM, Tucci S & Davies TF. Limited genetic susceptibility to severe Graves' ophthalmopathy: no role for CTLA-4 but evidence for an environmental etiology. *Thyroid* 2000 **10** 791–798.
- 5 Bartley GB. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. *Transactions of the American Ophthalmology Society* 1994 **92** 477–588.
- 6 Rivkees SA. Management of Graves' disease in children. In *Graves' Disease – Pathogenesis and Treatment*, pp 185–203. Eds B Rapoport & SM McLachlan. Boston: Kluwer Academic Publishers, 2000.

- 7 Marcocci C, Bartalena L, Bogazzi F, Panicucci M & Pinchera A. Studies on the occurrence of ophthalmopathy in Graves' disease. *Acta Endocrinologica* 1989 **120** 473–478.
- 8 Perros P, Crombie AL, Matthews JNS & Kendall-Taylor P. Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid–eye clinic. *Clinical Endocrinology* 1993 **38** 367–372.
- 9 Hagg E & Asplund K. Is endocrine ophthalmopathy related to smoking? *British Medical Journal* 1987 **295** 634–635.
- 10 Bartalena L, Bogazzi F, Tanda ML, Manetti L, Dell'Unto E & Martino E. Cigarette smoking and the thyroid. *European Journal of Endocrinology* 1995 **133** 507–512.
- 11 Bartalena L, Martino E, Marcocci C, Bogazzi F, Panicucci M, Velluzzi F, Loviselli A & Pinchera A. More on smoking habits and Graves' ophthalmopathy. *Journal of Endocrinological Investigation* 1989 **12** 733–737.
- 12 Prummel MF & Wiersinga WM. Smoking and risk of Graves' disease. *JAMA* 1993 **269** 479–482.
- 13 Pfeilschifter J & Ziegler R. Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs lifetime cigarette consumption. *Clinical Endocrinology* 1996 **45** 477–481.
- 14 Bartalena L, Marcocci C, Tanda ML, Manetti L, Dell'Unto E, Bartolomei MP, Nardi M, Martino E & Pinchera A. Cigarette smoking and treatment outcomes in Graves' ophthalmopathy. *Annals of Internal Medicine* 1998 **129** 632–635.
- 15 Metcalfe RA & Weetman AP. Stimulation of extraocular muscle fibroblasts by cytokines and hypoxia: possible role in thyroid-associated ophthalmopathy. *Clinical Endocrinology* 1994 **40** 67–72.
- 16 Prummel MF, Wiersinga WM, Mourits MP, Koornneef L, Berghout A & van der Gaag R. Amelioration of eye changes of Graves' ophthalmopathy by achieving euthyroidism. *Acta Endocrinologica* 1989 **121** 185–189.
- 17 Prummel MF, Wiersinga WM, Mourits MP, Koornneef L, Berghout A & van der Gaag R. Effect of abnormal thyroid function on the severity of Graves' ophthalmopathy. *Archives of Internal Medicine* 1990 **150** 1098–1101.
- 18 DeGroot LJ, Mangklabruks A & McCormick M. Comparison of RA131I treatment protocols for Graves' disease. *Journal of Endocrinological Investigation* 1990 **13** 111–118.
- 19 Karlsson AF, Westermark K, Dahlberg PA, Jansson R & Enoksson P. Ophthalmopathy and thyroid stimulation. *Lancet* 1989 **2** 691.
- 20 Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, Bruno-Bossio G, Nardi M, Bartolomei MP, Lepri A, Rossi G, Martino E & Pinchera A. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *New England Journal of Medicine* 1998 **338** 73–78.
- 21 Marcocci C, Bruno-Bossio G, Manetti L, Tanda ML, Miccoli P, Iacconi P, Bartolomei MP, Nardi M, Pinchera A & Bartalena L. The course of Graves' ophthalmopathy is not influenced by near total thyroidectomy. *Clinical Endocrinology* 1999 **51** 503–508.
- 22 Wiersinga WM. Preventing Graves' ophthalmopathy. *New England Journal of Medicine* 1998 **338** 121–122.
- 23 Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A & Pinchera A. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. *New England Journal of Medicine* 1989 **321** 1349–1352.
- 24 Tallstedt L, Lundell G, Topping O, Wallin G, Ljunggren J-G, Blomgren H, Taube A & the Thyroid Study Group. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. *New England Journal of Medicine* 1992 **326** 1733–1738.
- 25 Gorman CA. Radioiodine does not aggravate Graves' ophthalmopathy. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 340–342.
- 26 Marcocci C, Bartalena L, Bogazzi F, Bruno-Bossio G & Pinchera A. Relationship between Graves' ophthalmopathy and type of treatment of Graves' hyperthyroidism. *Thyroid* 1992 **2** 171–178.
- 27 Perros P & Kendall-Taylor P. Natural history of thyroid eye disease. *Thyroid* 1998 **8** 423–425.
- 28 Wiersinga WM. Graves' ophthalmopathy. *Thyroid International* 1997 **3** 1–15.
- 29 Vitti P, Rago T, Chiovato L, Pallini S, Santini F, Fiore E, Rocchi R, Martino E & Pinchera A. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. *Thyroid* 1997 **3** 369–375.
- 30 Weetman AP & Harrison BJ. Ablative or non-ablative therapy for Graves' hyperthyroidism in patients with ophthalmopathy? *Journal of Endocrinological Investigation* 1998 **21** 472–475.
- 31 Marcocci C, Bartalena L & Pinchera A. Ablative or non-ablative therapy for Graves' hyperthyroidism in patients with ophthalmopathy? *Journal of Endocrinological Investigation* 1998 **21** 468–471.
- 32 DeGroot LJ & Benjasuratwong Y. Evaluation of thyroid ablative therapy for ophthalmopathy of Graves' disease. *Orbit* 1996 **15** 187–196.
- 33 Weetman AP & Wiersinga WM. Current management of thyroid-associated ophthalmopathy in Europe. Results of an international survey. *Clinical Endocrinology* 1998 **49** 21–28.
- 34 Bartalena L, Marcocci C & Pinchera A. Radioiodine therapy and Graves' ophthalmopathy. In *Graves' Disease – Pathogenesis and Treatment*, pp 279–288. Eds B Rapoport & SM McLachlan. Boston: Kluwer Academic Publishers, 2000.
- 35 Tallstedt L, Lundell G, Blomgren H & Bring J. Does early administration of thyroxine reduce the development of Graves' ophthalmopathy after radioiodine treatment? *European Journal of Endocrinology* 1994 **130** 494–497.
- 36 Keltner JL. Is Graves' ophthalmopathy a preventable disease? *Archives of Ophthalmology* 1998 **116** 1106–1107.
- 37 Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF & Wiersinga WM. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the Medical Outcomes Study Instrument. *Thyroid* 1997 **7** 885–889.

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