

Graves' ophthalmopathy: natural history and treatment outcomes

Daniel Noth, Mathias Gebauer, Bruno Müller, Ulrich Bürgi, Peter Diem

Division of Endocrinology and Diabetes, University of Bern, Inselspital, Bern, Switzerland

Summary

Background: The pathogenesis of Graves' ophthalmopathy has not been yet clarified, and from a therapeutic standpoint Graves' ophthalmopathy remains an enigma. The natural course and effects of different treatment regimens are poorly documented.

Results: The mean observation period was 3.23 years (1–8.9 years) for all 196 patients, and 2.85 years (1–8.9 years) for the 81 patients with Graves' ophthalmopathy. The gender distribution was 77% female and 23% male in patients with Graves' disease and ophthalmopathy, and 81% female and 19% male in those patients without ophthalmopathy ($p = 0.57$). Seventy per cent of the patients developed Graves' ophthalmopathy within 12 months before or after the onset of the hyperthyroidism. Among the 81 patients with ophthalmopathy 53 (65%) received no therapy or only local protective agents. Twenty-five of these patients improved substantially, 26 did not change, and 2 deteriorated progressively. These results

were independent of the severity of the EO ($p = 0.42$). Among the 11 patients initially treated with systemic corticosteroids 7 improved, 3 did not change, and 1 worsened. Five patients received initially orbital irradiation. Three improved and 2 did not change after radiotherapy. Orbital decompression was performed in 3 patients. Nine patients received a combination treatment.

Conclusion: In conclusion, our study of a relatively large patient sample revealed the known epidemiological facts regarding Graves' disease and endocrine ophthalmopathy. The majority of patients needed no therapy or only local protective agents, and 47% improved spontaneously. Systemic corticosteroids and orbital irradiation appear to be equally effective as initial treatment in patients with more severe forms of Graves' ophthalmopathy.

Key words: Graves' disease; Graves' ophthalmopathy; thyreotoxicosis; treatment outcome

Introduction

Endocrine ophthalmopathy (EO) is an autoimmune disease, characterised by inflammation in the para- and retrobulbar area (involving connective tissue, fat, as well as muscle tissue) [1–4]. Eye involvement in Graves' disease is clinically evident in 25–50% of patients [5], but computed tomography, MRI, or B-scan ultrasonography identify asymptomatic optic nerve involvement in up to 90% of patients with Graves' disease [6–8]. Endocrine ophthalmopathy is also found, albeit seldom, in patients with Hashimoto's thyroiditis (chronic autoimmune thyroiditis), and with Graves' disease without hyperthyroidism [9–11].

Newer studies have brought possible significant insights to the understanding of the pathogenesis of EO. It has been found that TSH-receptors are also present in retrobulbar tissue [12–14], which is why it is suspected that TSH-receptor antibodies contribute to the development of EO by the stimulation of these retro-orbital tissue

TSH-receptors. Recently it was discovered that cytokines, e.g. tumor necrosis factor-alpha, interferon-gamma, interleukin 6 as well as transforming growth factor-beta, modify the expression of TSH receptors in the orbits, and encourage the differentiation of orbital fibroblasts and preadipocytes to adipocytes. This could be the reason why increased expression of TSH-receptors is seen as a key reason for the orbital tissue expansion [15–17].

Mild forms of EO may be sufficiently treated with symptomatic therapeutic interventions or local protective agents (elevation of the head of the bed, diuretics, eye drops). The main goal is the achievement and maintenance of an euthyroid state [18]. These measures alone are sufficient in many cases, because the majority of patients with EO demonstrate a favourable and often spontaneous self-limiting clinical course. In addition, all patients with Graves' disease should immediately

stop smoking [19–23]. The following treatment modalities are available in patients with severe EO: systemic corticosteroids given orally or parenterally, retrobulbar irradiation (high-voltage orbital irradiation), microsurgical orbital liposuction, surgical orbital decompression, immunosuppressive agents such as cyclosporine, plasmapheresis, i.v. gammaglobulins, or a combination of these therapeutic options. The choice of therapy needs to be

individualised. There is a lack of prospective controlled trials, and the data on the outcome of treatment regimens in unselected patient groups is insufficient. We therefore examined a large number of patients with Graves' disease retrospectively for the prevalence of EO, as well as the influence of various forms of therapy on EO in different age and gender groups.

Patients and methods

Consecutive patients with newly diagnosed Graves' disease ($n = 196$), examined and managed for a period of at least 1 year in the Division of Endocrinology and Diabetes of the University Hospital, Bern, Switzerland, between 1.1.1991 and 30.9.1998, were included in the study sample. The diagnosis of Graves' disease is based on clinical findings, chemical laboratory results (TSH, free T_4 , free T_3 , thyroid autoantibodies, especially thyrotropin receptor and thyreoperoxidase antibodies), and as far as possible sonographic (thyroid) and occasionally iodine-131 scan findings. Free T_4 was measured by means of luminescent immunoassay by the firm CIBA-Corning until 15.1.1994, and thereafter by chemical luminescence (Chiron Diagnostics). Free T_3 was examined by means of radioimmunoassay (Amersham) until 30.4.94, by enzymatic immunoassay (Abbott) from 1.5.94 to 31.5.94, and thereafter by means of chemical luminescence (Chiron Diagnostics). The TSH results were determined by means of immunoradiometric assay (Henning) until 15.1.1994, and thereafter by means of chemical luminescence (Chiron Diagnostics). The results of the TSH-receptor antibodies were determined by means of the TRAK-Assay[®] radioreceptorassay (Brahms Diagnostica GmbH).

Diagnosis of EO in patients with Graves' disease is based on typical clinical eye signs including eyelid

swelling, chemosis, tearing, corneal erosions or ulcerations, abnormal eye motility, exophthalmos (Hertel-exophthalmometry), and in part on imaging studies (CT or MRI of the orbits). In euthyroid patients diagnosis of EO is made using the diagnostic criteria of Bartley et al. [24], i.e. lid retraction plus at least one of the following findings: exophthalmos, signs of optic neuropathy, and significant ocular motility deficits.

The classification of EO was determined by a board approved endocrinologist or ophthalmologist and is based on the classification by the American Thyroid Association from Werner's [25] (table 1).

Only patients with stage 2 or higher EO were included in the study, as the symptoms of stage 1 could also be the result of hyperactivity of the sympathetic nervous system and are not necessarily an expression of an immunogenic ophthalmopathy.

Patients in whom the disease history only indicated suspected exophthalmos, and in whom the diagnosis was not confirmed by Hertel-exophthalmometry, as well as patients with non-specific eye symptoms (e.g. mild burning of the eyes or mild retrobulbar pressure sensation) were placed in the "questionable EO" group.

EO was judged to be improved or worsened when at least one of the following criteria was present:

- regression or progression of exophthalmos ≥ 2 mm (Hertel-exophthalmometry);
- changes in the inflammatory symptoms and signs;
- regression or progression of diplopia;
- improvement or deterioration of vision.

The above mentioned data were obtained by reviewing patient medical records. Statistical analysis was performed using the StatView[®] statistical software package (Version 4.5, SAS Institute Inc., Cary, North Carolina, USA). Fisher's exact, unpaired t-test, and ANOVA were used as appropriate. A p-value < 0.05 was considered significant.

Table 1
Classification of Graves' ophthalmopathy by Werner.

0	No symptoms or signs
1	Signs only, no symptoms (signs consist of upper lid retraction, staring vision, lid lag)
2	Soft tissue involvement (symptoms and signs)
3	Exophthalmos
4	Extraocular muscle involvement
5	Corneal involvement
6	Loss of vision (optic neuropathy)

Results

Of the 196 patients included (157 female, 39 male) with Graves' disease, 88 (45%) did not have EO, 81 (41%) had EO, and 27 (14%) were placed in the questionable EO category.

Of the 81 patients with EO, 3 patients had euthyroid Graves' disease, which indicates that they were euthyroid for the entire duration of the observation period. The mean observation period in these 3 cases was 2 years. In comparison the mean observation period for all 196 patients was 3.24

years (1.0–8.9), and 2.85 years (1.0–8.9) for all 81 patients with Graves' disease and EO. Sixty-two (77%) of the patients with Graves' disease and EO were female, 19 (23%) were male. In patients with Graves' disease without EO 93 (81%) were female, 22 male (19%). The difference in these ratios was not statistically significant ($p = 0.47$).

The average age of the patients with hyperthyroidism without EO was 41.9 years (21 to 81 years), and 41.6 years (16 to 77 years) in patients

Table 2
Applied therapy with EO stage.

Therapy	no/local	C	RT	C+RT	C+D	C+RT+D	D
Total	53	11	5	7	1	1	3
Stage 2*	12	1	0	1	0	0	0
Stage 3*	33	3	3	4	0	0	1
Stage 4*	7	7	2	2	0	1	2
Stage 5*	1	0	0	0	1	0	0

C = corticosteroids; RT = radiotherapy of the orbits;
D = surgical orbital decompression
* according to Werner

Table 3
Results of different treatment regimens.

Therapy	no/local	C	RT	C+RT	C+D	C+RT+D	D
Total (n)	53	11	5	7	1	1	3
Regression	11	5	3	4	1	1	1
Remission	14	2	0	0	0	0	2
Unchanged	26	3	2	3	0	0	0
Worsening	2	1	0	0	0	0	0

with hyperthyroidism and EO. In patients with euthyroid Graves' disease, the average age was 43.3 years (27-71). Differences were statistically not significant (p = 0.97, ANOVA).

In 55 patients (70%) EO presented in the same year as hyperthyroidism was diagnosed, in 11 patients (14%) EO occurred in the year following the diagnosis of hyperthyroidism, and in 10 patients (13%) EO presented over 2 years after the occurrence of hyperthyroidism. In 2 patients (3%), EO was detected more than one year before the manifestation of hyperthyroidism, and in no patient more than 2 years before the manifestation of hyperthyroidism.

Concerning the degree of EO, 14 patients (17%) had purely inflammatory signs (stage 2 according to Werner), 44 (54%) exophthalmos only (stage 3), 21 (26%) diplopia only (stage 4), and 2 patients (3%) cornea erosion or corneal ulceration (stage 5). Clinically detectable optic nerve neuropathy based on visual deterioration and visual field defects if recorded was not seen in any patient.

Of the 81 patients with EO, 53 were not treated or treated with local methods only (artificial tear fluid, anti-inflammatory eye drops), 11 were treated with systemic corticosteroid therapy, 5 with retrobulbar irradiation, and 3 with primary surgical orbit decompression. Of the 11 primarily treated with systemic corticosteroids, 6 had an un-

satisfactory result and radiotherapy was added as an additional treatment method. One patient was treated with additional systemic corticosteroids after irradiation because there was no improvement. In one patient after corticosteroid monotherapy and in one patient after the combination of systemic corticosteroids and irradiation, surgical orbital decompression was performed because of unsatisfactory clinical results. Oral corticosteroid therapy was still given for a maximal period of 3 months in a dose of 20-60 mg prednisone equivalent per day. Retrobulbar irradiation comprised 10 sessions at 2 Gray/day and not exceeding a total dose of 20 Gray.

In table 2 an indication is given of which form of therapy was applied for each stage of EO. Systemic corticosteroid therapy was preferred for EO stage 4, compared to radiotherapy. Retrobulbar irradiation alone, and retrobulbar irradiation in addition to primary corticosteroid therapy was given mainly to patients with EO stages 3 and 4.

When looking at the patient group as a whole, including specifically treated as well as non-treated patients, the EO course of disease in 34 patients (42%) was stationary, progressive in 3 (4%), regressive in 26 (32%), and in 18 (22%) it resulted in full remission.

Of the 53 patients with EO who received only local therapy, 25 showed substantial improvement, 26 did not change, and 2 progressively deteriorated. An additional therapy with systemic corticosteroids and a radiotherapy were refused by these 2 patients. Systemic corticosteroid monotherapy lead to substantial recovery in 7 of 11 patients. If the patients were included to receive additional retrobulbar radiotherapy due to unsatisfactory response to corticosteroid monotherapy alone (6 patients), as well as orbital decompression after radiotherapy (1 patient), corticosteroid therapy lead to substantial improvement or remission in 7 of 19 patients. Primary radiotherapy was effective in 3 of 5 patients, and in 3 out of 7 patients if the patients were included to receive additional systemic corticosteroids and radiotherapy in conjunction with orbital decompression. After ineffective systemic corticosteroid therapy, 4 of 6 patients that required additional radiotherapy of the orbits showed satisfactory improvements. Table 3 shows the results of different treatment regimens on the outcome of EO disease, table 4 the relation between treatment regimens, severity of disease and success rate.

Discussion

Our study, conducted with a relatively large number of patients, gave the following epidemiological results. Graves' hyperthyroidism occurs predominantly in females, the f:m ratio being 4.2:1 in our patient sample. In the group of patients with Graves' hyperthyroidism and ophthalmopathy, the

f:m ratio was smaller (3.3:1), but this difference was not statistically significant. This leads to the conclusion that the female sex is a risk factor for the development of Graves' hyperthyroidism on the one hand, but on the other hand that the relative risk for ophthalmopathy in cases with Graves' hy-

Table 4

Relation between treatment regimens, severity of disease and success rate.

classification	n	regression	remission	unchanged	worsening
<i>A: no or only local therapy (n = 53)</i>					
stage 2*	12	1	5	5	1
stage 3*	33	7	8	18	0
stage 4*	7	2	1	3	1
stage 5*	1	0	1	0	0
<i>B: systemic corticosteroids (n = 11)</i>					
stage 2*	1	0	1	0	0
stage 3*	3	2	0	0	1
stage 4*	7	3	1	3	0
stage 5*	0	0	0	0	0
<i>C: orbital irradiation (n = 5)</i>					
stage 2*	0	0	0	0	0
stage 3*	3	2	0	1	0
stage 4*	2	1	0	1	0
stage 5*	0	0	0	0	0
<i>D: systemic corticosteroids and orbital irradiation (n = 7)</i>					
stage 2*	1	0	0	1	0
stage 3*	4	3	0	1	0
stage 4*	2	1	0	1	0
stage 5*	0	0	0	0	0
<i>E: surgical orbital decompression (n = 3)</i>					
stage 2*	0	0	0	0	0
stage 3*	1	0	1	0	0
stage 4*	2	1	1	0	0
stage 5*	0	0	0	0	0
<i>F: corticosteroids and surgical orbital decompression (n = 1)</i>					
stage 5*	1	1	0	0	0
<i>G: corticosteroids, radiotherapy and surgical orbital decompression (n = 1)</i>					
stage 4*	1	1	0	0	0

* according to Werner

perthyroidism is independent of gender. This is in agreement with studies of Perros et al. [26] with a similar f:m ratio of 4.05:1 in patients with Graves' disease and EO. In contrast, the quotient was significantly lower in patients with Graves' hyperthyroidism with EO, than in those with Graves' hyperthyroidism without EO, as reported by Marcocci et al. (2.1 vs. 3.4) [27].

The age distribution demonstrated almost identical average ages in patients with Graves' disease with or without ophthalmopathy. Similarly Marcocci et al. [27] demonstrated in a study of 221 patients with EO and 274 patients without ophthalmopathy, that the age distribution also was identical in both groups. Apparently, the patient age therefore does not contribute to an increase in the risk for ophthalmopathy.

In 81 or 85% of cases with Graves' disease and ophthalmopathy, the ophthalmopathy occurred within an interval of 18 months prior or after manifestations of the Graves' hyperthyroidism [27, 28]. In our study Graves' hyperthyroidism and ophthalmopathy were diagnosed in the same year in 70% of patients.

Three of the 81 patients with ophthalmopathy had euthyroid Graves' disease, defined as endocrine ophthalmopathy without hyperthyroidism (and without Hashimoto's hypothyroidism). The observation period in these cases was on average only 2 years. It is known, however, that in up to 5% of cases with Graves' disease hyperthyroidism manifests 3 or more years after the onset of ophthalmopathy [28]. Euthyroid Graves' disease was seen in 19 of 221 patients (8.6%) in a study by Marcocci et al., whereas Gorman et al. found euthyroid Graves' disease in 29 of 194 patients (15%). In the study by Marcocci et al. the observation period was between 3 and 13 years, while in the study by Gorman et al. this period was <3 years in 22 of the 29 patients, explaining the relatively high patient number with euthyroid Graves' disease. More authors found increased levels of thyroid autoantibodies (especially thyrotropin receptor and thyreoperoxidase antibodies), and decreased TSH levels after TRH stimulation tests and/or a depressed suppression of iodine-131 uptake after treatment with triiodothyronine [10, 11, 27, 29, 30] in patients with euthyroid Graves' dis-

ease. In our study elevated thyrotropin receptor and thyreoperoxidase antibodies were found in only one of the 3 patients with euthyroid Graves' disease. TRH-stimulation and triiodothyronine suppression tests were not performed in these patients.

Clinically detectable optic neuropathy (ON) is found on average in 3–5% of the patients with endocrine ophthalmopathy [5, 21, 32]. Visual impairment is the main symptom of ON. However, other methods used to detect optic neuropathy are more sensitive than vision tests alone and also take into consideration early forms of optic nerve damage [33, 34]. Using visual evoked cortical potentials (VECP) Salvi et al. found signs indicative of optic neuropathy in 21 out of 88 patients (23.8%) [31]. Considering the high prevalence of optic neuropathy found by these authors, it is surprising that optic neuropathy was not seen in any of our patients. However, the diagnosis of optic neuropathy in our patients was based on clinical examination only, based on visual deterioration and visual field defects. More sensitive methods were not available. Therefore, in our study the actual occurrence of optic neuropathy is probably underestimated. Furthermore the question arises whether patients with obvious symptoms of optic neuropathy would have been referred elsewhere.

The pathogenesis of optic neuropathy is known. As a result of inflammatory swelling of the interior of the orbit, especially of extraocular connective tissue, fat and muscle tissue at the apex of the orbit, compression of the optic nerve may arise leading to optic neuropathy [33]. This process does not always lead to exophthalmos which means that optic neuropathy may also occur in the absence of exophthalmos [5, 35, 36].

In our sample, 25 of the 53 patients who received no treatment or eye drops only, demonstrated partial or total regression of endocrine ophthalmopathy, and therefore had a favourable spontaneous outcome. A descriptive study done by Perros et al. showed the natural course of endocrine ophthalmopathy. This study analysed 101 patients who were seen at a centre specialising in endocrine ophthalmopathy in Newcastle upon Tyne, UK, during a 5-year period. In 59 of the 101 patients no indication existed for specific endocrine ophthalmopathy treatment. This subgroup was observed for an average of 12 months. In 13 of these 59 patients (22%) a significant spontaneous improvement was seen, and in 25 (42.4%) moderate spontaneous improvement was seen during this time. In 13 patients (22%) the disease course was stable during the observation period, while progressive deterioration was seen in 8 patients (13.5%) in whom immunosuppressive therapy needed to be used [37].

In our patient sample systemic corticosteroids were given orally in a total of 19 patients, in 11 patients as a monotherapy, in 6 patients in combination with orbital irradiation, in one patient combined with surgical decompression, and in a fur-

ther patient with irradiation/surgery. Systemic corticosteroids were effective in 7 of the total of 19 patients (39%). Numerous other studies have indicated a positive effect of oral systemic steroid therapy on endocrine ophthalmopathy in 33% to 61% [38–40]. Given parenterally and in high doses (up to 1 g methylprednisone/day) corticosteroids improved EO in 73 to 78% of the patients [41, 42].

The somewhat disappointing success of systemic corticosteroid therapy in our study may be related to the fact that none of our patients received parenteral corticosteroid therapy. Furthermore, corticosteroid therapy was given in relatively low doses of 20 to 60 mg prednisone equivalents per day compared to the studies by Prummel et al. and Bartalena et al. using respectively 60 mg prednisone equivalent and 70–80 mg methylprednisone per day [38–40].

However, it is important to note that systemic corticosteroid therapy was insufficient in 4 of 10 patients (40%) in whom endocrine ophthalmopathy had already been present for more than one year. Similarly, other studies have shown that little effect is seen on endocrine ophthalmopathy by systemic corticosteroids or radiotherapy if the disease was present for more than one year [40, 42, 43]. A long latent period between manifestation of endocrine ophthalmopathy and the initiation of therapy also leads to an unfavourable response to treatment. This latency is problematic in our centre since we have little control over referral practices.

In our study, retrobulbar irradiation was successful in 3 of 5 patients. Other studies showed improvement of radiotherapy with EO symptoms in 46–65% of cases [38, 43]. In a controlled, randomised, double-blind study of 28 patients, Prummel et al. showed that orbital irradiation was equally effective as oral steroid therapy. The efficacy in both treatment groups was 50% [38]. The study also showed that although soft tissue signs and eye muscle motility improved with both forms of therapy, exophthalmos did not. On the basis of the available data systemic corticosteroids and radiotherapy can be regarded as equivalent therapy options in those patients in whom endocrine ophthalmopathy presents with predominantly soft tissue and eye muscle abnormalities. A further treatment possibility would be a combination of both methods, increasing the efficacy of therapy up to 75% [40, 44].

As hyperthyroidism per se could worsen an existing endocrine ophthalmopathy due to the hyperactivity of the sympathetic nervous system [4, 5, 18, 37, 45, 46], euthyroidism should be achieved through thionamide treatment as soon as possible. Ideally this should be done even before the onset of specific EO therapy. If, however, severe optic neuropathy or severe exophthalmos with corneal ulceration and threatening perforation were present, surgical decompression of the orbits should be performed, even before euthyroidism is fully achieved [4, 47–49].

In our study a total of 5 patients underwent

surgical treatment. The indication in one case was corneal damage, and in the remaining 4 patients orbital decompression was done for diplopia and exophthalmos. The diplopia persisted after orbital decompression in these patients, and a second operative procedure had to be performed to correct strabism. The persistence or new development of diplopia after surgery is a well-known complication [4, 50]. Corneal involvement with EO alone is not an absolute indication for surgery. The degree of corneal damage is the determining factor. In one of our two patients with stage 5 EO, corneal erosions healed with local therapy only.

Our study has some meaningful limitations. First, there is a relatively small number of severe cases, so we can't draw definitive conclusions about the treatment of these patients. Second, it is a retrospective study with typical limitations in relation to the strength, for example for the detection of optic neuropathy. Furthermore, not all of our patients obtained regular ophthalmologic controls by an ophthalmologist. Ideally, patients with Graves' ophthalmopathy should be randomised receiving either no or only local therapy, corticosteroids given orally or parenterally at a defined dosage over a defined time period, radiotherapy, or combination therapy with corticosteroids and radiotherapy. The object of such a study is to find out suitable answers to important questions such as when, at which dosage or by which route to start therapy with systemic corticosteroids, or whether

combination therapy with corticosteroids and orbital irradiation is superior to monotherapy, and at which time surgical decompression of the orbits should be performed.

In conclusion, our study of a relatively large patient sample revealed the known epidemiological facts regarding Graves' disease and endocrine ophthalmopathy. Our results corresponded with numerous other studies showing that the majority of patients needed no therapy or only local protective agents, and that 47% improved spontaneously. More severe forms of EO might be treated satisfactorily with systemic oral therapy or radiotherapy.

The most severe forms of EO, e.g. severe ocular signs, cosmetically unacceptable exophthalmos, optic neuropathy and threatening blindness, corneal ulceration or perforation, are fortunately seldom seen. These are indications for surgery by an experienced orbital surgeon. The treatment of complex cases of EO necessitates cooperation between endocrinologists, ophthalmologists, radiotherapists, and surgeons specialising in orbital procedures.

Correspondence:

Dr. med. Daniel Noth

Medizinische Klinik

Spital Interlaken

CH-3800 Interlaken

e-mail: danielnoth@spitalinterlaken.ch

References

- 1 Heufelder AE, Spitzweg C. Pathogenesis of immunogenic hyperthyroidism and endocrine orbitopathy. *Internist* 1998;39:599-606.
- 2 Stadlmayr W, Spitzweg C, Bichlmair AM, Heufelder AE. TSH receptor transcripts and TSH receptor-like immunoreactivity in orbital and pretibial fibroblasts of patients with Graves' ophthalmopathy and pretibial myxedema. *Thyroid* 1997;7:3-12.
- 3 Bahn RS, Heufelder AE. Pathogenesis of Graves' ophthalmopathy. *N Engl J Med* 1993;329:1468-75.
- 4 Bahn RS, Garrity JA, Gorman CA. Clinical review 13: Diagnosis and management of Graves' ophthalmopathy. *J Clin Endocrinol Metab* 1990;71:559-63.
- 5 Jacobson DH, Gorman CA. Diagnosis and management of endocrine ophthalmopathy. *Med Clin North Am* 1984;69:973-88.
- 6 Forrester JV, Sutherland GR, McDougall IR. Dysthyroid ophthalmopathy: orbital evaluation with B-scan ultrasonography. *J Clin Endocrinol Metab* 1977;45:221-4.
- 7 Enzmann D, Marshal WH Jr, Rosenthal AR, Kriss JP. Computed tomography in Graves' ophthalmopathy. *Radiology* 1976;118:615-20.
- 8 Werner SC, Coleman DJ, Franzen LA. Ultrasonographic evidence of a consistent orbital involvement in Graves' disease. *N Engl J Med* 1974;290:447-50.
- 9 Teng CS, Yeo PP. Ophthalmic Graves's disease: natural history and detailed thyroid function studies. *Br Med J* 1977;1:273-5.
- 10 Solomon DH, Chopra IJ, Chopra U, Smith FJ. Identification of subgroups of euthyroid Graves' ophthalmopathy. *N Engl J Med* 1977;296:181-6.
- 11 Hall R, Kirkham K, Doniach D, el-Kabir D. Ophthalmic Graves' disease. Diagnosis and pathogenesis. *Lancet* 1970;1:375-8.
- 12 Major BJ, Cures A, Frauman AG. The full length and splice variant thyrotropin receptor is expressed exclusively in skeletal muscle of extraocular origin: a link to the pathogenesis of Graves' ophthalmopathy. *Biochem Biophys Res Commun* 1997;230:493-6.
- 13 Heufelder AE. Involvement of the orbital fibroblast and TSH receptor in the pathogenesis of Graves' ophthalmopathy. *Thyroid* 1995;5:331-40.
- 14 Feliciello A, Porcellini A, Ciullo I, Bonavolonta G, Avvedimento EV, Fenzi G. Expression of thyrotropin-receptor mRNA in healthy and Graves' disease retro-orbital tissue. *Lancet* 1993;342:337-8.
- 15 Valyasevi RW, Jyonouchi SC, Dutton CM, Munsakul N, Bahn RS. Effect of tumor necrosis factor-alpha, interferon-gamma, and transforming growth factor-beta on adipogenesis and expression of thyrotropin receptor in human orbital preadipocyte fibroblasts. *J Clin Endocrinol Metab*. 2001;86:903-8.
- 16 Crisp M, Starkey KJ, Lane C, Ham J, Ludgate M. Adipogenesis in thyroid eye disease. *Invest Ophthalmol Vis Sci* 2000;41:3249-55.
- 17 Wakelkamp IM, Gerding MN, Van Der Meer JW, Prummel MF, Wiersinga WM. Both Th1- and Th2-derived cytokines in serum are elevated in Graves' ophthalmopathy. *Clin Exp Immunol*. 2000;121:453-7.
- 18 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. *Arch Intern Med* 1990;150:1098-101.
- 19 Bartalena L, Bogazzi F, Tanda ML, Manetti L, Dell'Unto E, Martino E. Cigarette smoking and the thyroid. *Eur J Endocrinol* 1995;133:507-12.
- 20 Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. *JAMA* 1993;269:479-82.

- 21 Shine B, Fells P, Edwards OM; Weetman AP. Association between Graves' ophthalmopathy and smoking. *Lancet* 1990;335:1261-3.
- 22 Bartalena L, Martino E, Marcocci C, Bogazzi F, Panicucci M, Velluzzi F, et al. More on smoking habits and Graves' ophthalmopathy. *J Endocrinol Invest* 1989;12:733-7.
- 23 Hagg E; Asplund K. Is endocrine ophthalmopathy related to smoking? *Br Med J* 1987;295:634-5.
- 24 Bartley GB, Gorman CA. Diagnostic criteria for Graves' ophthalmopathy. *Am J Ophthalmol Jun* 1995;119:792-5.
- 25 Werner SC. Classification of the eye changes of Graves' disease. *J Clin Endocrinol Metab* 1969;29:982-4.
- 26 Perros P, Crombie AL, Matthews JN, Kendall-Taylor P. Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid-eye clinic. *Clin Endocrinol* 1993;38:367-72.
- 27 Marcocci C, Bartalena L, Bogazzi F, Panicucci M, Pinchera A. Studies on the occurrence of ophthalmopathy in Graves' disease. *Acta Endocrinol* 1989;120:473-8.
- 28 Gorman CA. Temporal relationship between onset of Graves' ophthalmopathy and diagnosis of thyrotoxicosis. *Mayo Clin Proc* 1983;58:515-9.
- 29 Salvi M, Zhang ZG, Haegert D, Woo M, Liberman A, Cadarso L, et al. Patients with endocrine ophthalmopathy not associated with overt thyroid disease have multiple thyroid immunological abnormalities. *J Clin Endocrinol Metab* 1990;70:89-94.
- 30 Khoo DH, Eng PH, Ho SC, Tai ES, Morgenthaler NG, Seah LL, et al. Graves' ophthalmopathy in the absence of elevated free thyroxine and triiodothyronine levels: prevalence, natural history, and thyrotropin receptor antibody levels. *Thyroid* 2000;10:1093-100.
- 31 Salvi M, Spaggiari E, Neri F, Macaluso C, Gardini E, Ferrozzi F, et al. The study of visual evoked potentials in patients with thyroid-associated ophthalmopathy identifies asymptomatic optic nerve involvement. *J Clin Endocrinol Metab* 1997;82:1027-30.
- 32 Barth A, Bosshard C, Burgi U, Burgi H. Severe endocrine ophthalmopathy. A review with case reports. *Schweiz Med Wochenschr* 1991;121:3-9.
- 33 Neigel JM, Rootman J, Belkin RI, Nugent RA, Drance SM, Beattie CW, et al. Dysthyroid optic neuropathy. The crowded orbital apex syndrome. *Ophthalmology* 1988;95:1515-21.
- 34 Batch JA, Lepre F. Early diagnosis of Graves' optic neuropathy using visual evoked responses. *Postgrad Med J* 1990;66:664-6.
- 35 Gladstone GJ. Ophthalmologic aspects of thyroid-related orbitopathy. *Endocrinol Metab Clin North Am* 1998;27:91-100.
- 36 Hamburger JI, Sugar HS. What the internist should know about the ophthalmopathy of Graves' disease. *Arch Intern Med* 1972;129:131-9.
- 37 Perros P, Crombie AL, Kendall-Taylor P. Natural history of thyroid associated ophthalmopathy. *Clin Endocrinol* 1995;42:45-50.
- 38 Prummel MF, Mourits MP, Blank L, Berghout A, Koornneef L, Wiersinga WM. Randomized double-blind trial of prednisone versus radiotherapy in Graves' ophthalmopathy. *Lancet* 1993;342:949-54.
- 39 Prummel MF, Mourits MP, Berghout A, Krenning EP, van der Gaag R, Koornneef L et al. Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. *N Engl J Med* 1989;321:1353-9.
- 40 Bartalena L, Marcocci C, Chiovato L, Laddaga M, Lepri G, Andreani D et al. Orbital cobalt irradiation combined with systemic corticosteroids for Graves' ophthalmopathy: comparison with systemic corticosteroids alone. *J Clin Endocrinol Metab* 1983;56:1139-44.
- 41 Tagami T, Tanaka K, Sugawa H, Nakamura H, Miyoshi Y, Mori T, et al. High-dose intravenous steroid pulse therapy in thyroid-associated ophthalmopathy. *Endocr J* 1996;43:689-99.
- 42 Kendall-Taylor P, Crombie AL, Stephenson AM, Hardwick M, Hall K. Intravenous methylprednisolone in the treatment of Graves' ophthalmopathy. *BMJ* 1988;297:1574-8.
- 43 Donaldson SS, Bagshaw MA, Kriss JP. Supervoltage orbital radiotherapy for Graves' ophthalmopathy. *J Clin Endocrinol Metab* 1973;37:276-85.
- 44 Tsujino K, Hirota S, Hagiwara M, Fukada S, Takada Y, Hishikawa Y et al. Clinical outcomes of orbital irradiation combined with or without systemic high-dose or pulsed corticosteroids for Graves' ophthalmopathy. *Int J Radiat Oncol Biol Phys* 2000;48:857-64.
- 45 Solem JH, Seggaard E, Ytteborg J. The course of endocrine ophthalmopathy during antithyroid therapy in a prospective study. *Acta Med Scand* 1979;205:111-4.
- 46 Gorman CA. The presentation and management of endocrine ophthalmopathy. *Clin Endocrinol Metab* 1978;7:67-96.
- 47 Fells P. Thyroid-associated eye disease: clinical management. *Lancet* 1991;338:29-32.
- 48 Fells P. Orbital decompression for severe dysthyroid eye disease. *Br J Ophthalmol* 1987;71:107-11.
- 49 Trobe JD, Glaser JS, Laflamme P. Dysthyroid optic neuropathy. Clinical profile and rationale for management. *Arch Ophthalmol* 1978;96:1199-1209.
- 50 Goldberg RA, Perry JD, Hortalez V, Tong JT. Strabismus after balanced medial plus lateral wall versus lateral wall only orbital decompression for dysthyroid orbitopathy. *Ophthalm Plast Reconstr Surg* 2000;16:271-7.

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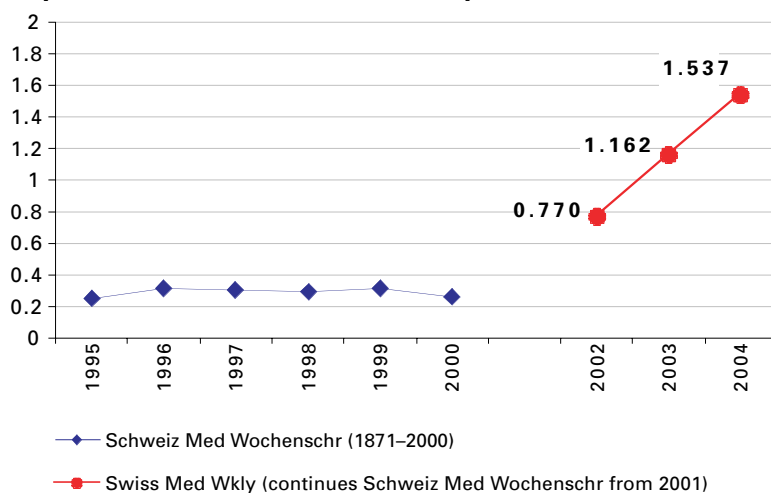
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