INVITED REVIEW

¹³¹I and thyroid-associated ophthalmopathy

Åse Krogh Rasmussen¹, Birte Nygaard² and Ulla Feldt-Rasmussen¹¹Medical Department of Endocrinology, Rigshospitalet and ²Medical Division of Endocrinology, Herlev Hospital, University of Copenhagen, Denmark

(Correspondence should be addressed to Å K Rasmussen, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark; Email: aakr@rh.dk)

Abstract

Objective: Radioiodine (¹³¹I) used to obtain euthyroidism in thyrotoxic patients is suspected of having a worsening or provoking effect on thyroid-associated ophthalmopathy (TAO), an autoimmune disease closely related to Graves' disease.

Design: This review summarises the existing literature and describes risk factors influencing the course of TAO including thyroid function, cigarette smoking and treatment of Graves' hyperthyroidism (especially ¹³¹I therapy).

Conclusion: It is recommended that patients who may be at a greater risk of worsening ophthalmopathy are considered when choosing the modality of therapy of hyperthyroidism and also in deciding whether prophylactic systemic glucocorticoid treatment is indicated.

European Journal of Endocrinology 143 155–160

Introduction

Thyroid-associated ophthalmopathy (TAO) is an autoimmune disorder closely associated with Graves' disease (GD). It may occur before the diagnosis of GD, although it mainly occurs concurrently with the onset of hyperthyroidism, but may even arise afterwards. The vast majority of patients with GD have evidence of TAO, and by CT or MR scan this is evident in up to 90% of the patients, even though apparent clinically in only 24–50% of patients (1). The pathogenetic mechanism behind TAO is still unclear. The thyroid tissue as a source of antigens may play a central role in the maintenance of ophthalmopathy (2). An autoimmune response against an autoantigen shared between the thyroid and the orbit has been suggested as a possible mechanism (reviewed in 3). However, the nature of the autoantigen(s) involved is not known, but a number of candidates have been suggested (reviewed in 4). Fibroblasts within the extraocular muscles may be activated by cytokines released by infiltrating lymphocytes (reviewed in 5). Immunohistochemical studies have demonstrated the presence of interferon (IFN)- γ , tumor necrosis factor (TNF)- α and interleukin (IL)-1 α within the retro-ocular tissues of patients with severe TAO (6). Phenotypic studies of orbital infiltrating T lymphocytes reveal that both CD4 and CD8 cells are present, and furthermore, both T helper type 1 (Th1) and type 2 (Th2) cells are represented. Glycosaminoglycans (GAG) are accumulated in retro-ocular connective tissues, and several cytokines (including IL-1 α , IFN- γ and transforming growth factor- α) have been

shown to be potent stimulators of *in vitro* GAG synthesis by retro-ocular fibroblasts (reviewed in 5). Furthermore, IL-1 receptor antagonists and soluble IL-1 receptors have been shown to inhibit GAG production (7).

Although not thoroughly documented, obtaining and maintaining euthyroidism is presumably important to improve eye manifestations. Radioiodine (¹³¹I) has been used to obtain euthyroidism; however, during the past 10 years an ¹³¹I treatment-associated worsening or activation of TAO has been argued (8), and results based on previous studies have been conflicting. However, recent prospective studies have provided new information, and in this review we summarise the currently available data.

Factors influencing TAO

Thyroid function

The risk of development or worsening of TAO has been shown to be increased with higher pretreatment serum tri-iodothyronine concentrations (9), suggesting that a more severe thyrotoxicosis may predict a higher risk of TAO. Karlsson *et al.* (10) evaluated 30 consecutive patients with GD complicated by severe TAO developed subsequent to the start of therapy (thyrostatic drugs in nine patients, surgery in six patients and radioactive iodine in 15 patients). In 15 of the patients, treatment-induced hypothyroid episodes were followed by an exacerbation of the eye disease. In a retrospective study of 90 patients with TAO, Prummel *et al.* (11)

also found that dysthyroidism was associated with more severe Graves' ophthalmopathy. Furthermore, Kung *et al.* (12) showed that development of hypothyroidism with rising thyrotropin (TSH) levels after ^{131}I therapy for GD was associated with a greater risk of development or exacerbation of ophthalmopathy. An increase in TSH might stimulate receptors in orbital tissues, leading to an exacerbation of eye disease. In the prospective study of Kung *et al.* (12), 114 patients with GD were randomized to either ^{131}I alone or adjunct medical treatment with methimazol and thyroxine. The incidence of development or exacerbation of TAO was similar in the two treatment groups. However, in a retrospective analysis early administration of thyroxine was shown to reduce the frequency of development or deterioration of TAO (13). It cannot be excluded, however, that a possible post-therapeutic hypothyroidism could explain the high prevalence of development/worsening of TAO among the ^{131}I -treated group in the study of Tallstedt *et al.* (9), as this group did not receive thyroxine unless the patients developed hypothyroidism. In contrast, the patients randomized to subtotal thyroidectomy or methimazol were all prophylactically treated with thyroxine to prevent hypothyroidism. In the study of Bartalena *et al.* (14) none of the patients were prophylactically treated with thyroxine in either group, and only in cases of hypothyroidism after ^{131}I treatment was thyroxine administered.

Tobacco smoking

An association between smoking and Graves' TAO has been shown (15–17). In the study of Tallstedt *et al.* (9) tobacco smoking was more common among the patients who had ophthalmopathy during the study. Bartalena *et al.* (18) have demonstrated that cigarette smoking increased the risk for progression of ophthalmopathy after radioiodine therapy and decreased the efficacy of glucocorticoid therapy. It has not been investigated whether cessation of smoking is beneficial once TAO has developed.

Influence of treatment of Graves' hyperthyroidism on the course of TAO

^{131}I therapy

^{131}I causes an injury of the thyroid tissue and thereby release of thyroid antigens. This has been illustrated by an increase in serum levels of thyroglobulin seen within the first days of ^{131}I treatment of patients with GD (19), an approximate 20% increase in T4 and T3 concentrations in serum within the first 2 weeks, and a compensatory decrease in serum TSH 3 weeks after ^{131}I treatment of multinodular toxic or non-toxic goitre (20, 21). An exaggerated immunological response can be seen in patients treated with ^{131}I for GD, in whom an increase in titers of TSH receptor antibodies (TRAb),

(22) and in thyroglobulin and thyroid peroxidase antibodies (23) was seen approximately 3 months after ^{131}I treatment. A similar immunological response has recently been shown in a lower proportion (approximately 5%) of patients treated with ^{131}I for nodular toxic as well as non-toxic goitre. In these patients an induction of a Graves'-like disease, including development of TRAb was seen 3–6 months after ^{131}I therapy (24–26). A similar induction of GD has been described related to subacute thyroiditis (27, 28) and ethanol injection of hyperfunctioning autonomous thyroid adenoma (29, 30), representing other treatments causing destruction of the thyroid cells and release of thyroid antigen. Accordingly, release of thyroid antigen has been demonstrated in relation to subacute thyroiditis (31) and in relation to thyroid resection for thyrotoxicosis or non-toxic goiter, a drastic increase in circulating levels of thyroglobulin was seen (32, 33). Theoretically a worsening/activation of TAO could be explained by a similar activation of the autoimmune response following injury of thyroid tissue, if a common autoantigen between the thyroid and the orbit exists. Soliman *et al.* (34) showed an increased T-cell response after ^{131}I therapy, measured as the proliferative responses of peripheral blood mononuclear cells and TSH receptor-specific T-cell lines to thyroid antigens. Thyroid cell damage may trigger activation of pre-existing autoimmunity.

A number of papers have reported that ^{131}I treatment of GD aggravates TAO (35–38; Table 1). However, in other studies this aggravation of TAO could not be demonstrated (39–42; Table 1). The discrepancies in the results might be due to an unequal distribution of smokers included in the different treatment groups in these studies; this point is not stated in details in the description of the patient materials in the studies. Furthermore, it may be a question of whether the patients had TAO prior to the treatment or not, and if TAO was in an active or a stable stage at the time of treatment.

Two larger prospective studies exist (9, 14) (Table 2). In the first study 114 patients with GD (18 patients (16%) with ophthalmopathy before treatment) aged between 35 and 55 years were openly randomized at the onset of hyperthyroidism to either subtotal thyroidectomy, medical antithyroid treatment or ^{131}I . Activation or worsening of TAO was seen in 16%, 10% and 33% respectively of the patients (9). In a very recent study, 443 patients with GD with or without mild ophthalmopathy were openly randomized at the onset of hyperthyroidism to receive either ^{131}I , ^{131}I followed by a 3-month course of prednisone, or methimazol for 18 months. Of the 150 patients with GD treated with ^{131}I , an activation/worsening of TAO was seen in 15% compared with 0% in the group of patients who received prednisone supplemental to ^{131}I (14). In a third recent prospective, yet small and unrandomized study in patients with GD (43), none of 22 non-smokers

Table 1 Influence of ¹³¹I treatment on TAO compared with other treatment modalities in retrospective studies.

Reference	Treatment	Activation/worsening (%)	n
Aranow <i>et al.</i> 1965 (42)	Antithyroid drugs	0	137
	Surgery	0	38
	¹³¹ I	0	24
Hamilton <i>et al.</i> 1967 (39)	Antithyroid drugs	—	—
	Surgery	6	232
	¹³¹ I	9	136
Kriss <i>et al.</i> 1967 (35)	Antithyroid drugs	—	—
	Surgery	—	—
	¹³¹ I	13	24
Barbosa <i>et al.</i> 1972 (36)	Antithyroid drugs	0	34
	Surgery	7	14
	¹³¹ I	4	72
Calissendorf <i>et al.</i> 1986 (40)	Antithyroid drugs	13	72
	Surgery	18	17
	¹³¹ I	0	36
Sridama & DeGroot 1989 (41)	Antithyroid drugs	12	182
	Surgery	11	164
	¹³¹ I	12	241
Vestergaard & Laurberg 1989 (37)	Antithyroid drugs	—	—
	Surgery	—	—
	¹³¹ I	12	50
Barth <i>et al.</i> 1991 (38)	Antithyroid drugs	—	—
	Surgery	—	—
	¹³¹ I	23	89
Vazquez-Chavez <i>et al.</i> 1992 (55)	Antithyroid drugs	—	—
	Surgery	35	20
	¹³¹ I	45	20

treated with radioiodine and eight treated with antithyroid drugs developed worsening in ophthalmopathy. Furthermore, the dose of radioiodine may play a role as it has been demonstrated that progression of exophthalmos was significantly less common among patients who became hypothyroid after the first dose, compared with those who continued to be thyrotoxic and had to be treated again (44). A history of multiple ¹³¹I therapies has also been associated with worsening of ophthalmopathy (44).

In patients treated with ¹³¹I for a toxic or non-toxic nodular goitre casuistic notes have recently described development of not only a Graves'-like hyperthyroidism with development of TRAb but also Graves' ophthalmopathy (45, 46).

Surgical therapy

Worsening of eye manifestations after surgical treatment of hyperthyroidism has also been demonstrated, albeit to a lesser degree after total thyroid ablation compared with subtotal thyroidectomy (reviewed in 47). In the prospective study of Tallstedt *et al.* (9), 16% of the patients developed activation or worsening of TAO after subtotal thyroidectomy (Table 2). The participants in this study, however, were only pretreated with propranolol, and no prospective data exist as to whether this deterioration was abolished, if the patients had undergone surgery in a controlled euthyroid phase, or had undergone total ablation of the thyroid gland. In an unrandomized prospective study of 45 patients with

Table 2 Influence of ¹³¹I treatment on TAO compared with other treatment modalities in two open randomized studies.

Reference	Treatment	Activation/worsening (%)	95% c.i.	n	Prophylactic T ₄ substitution
Tallstedt <i>et al.</i> 1992 (9)	Medical antithyroid drug	10	3–25	38	+
	Surgery (subtotal thyroidectomy)	16	6–32	37	+
	¹³¹ I	33	19–50	39	—
Follow-up: 24 months					
Bartalena <i>et al.</i> 1998 (14)	Medical antithyroid drug	3	1–7	148	—
	¹³¹ I	15	10–22	150	—
	¹³¹ I + steroids	0	0–2	145	—
Follow-up: 12 months					

Graves' ophthalmopathy, all of whom were pretreated with antithyroid drugs over a 1–3-year period (48), 21 patients were treated by subtotal thyroidectomy and the remainder with ^{131}I . GD ophthalmopathy improved to a greater extent after subtotal thyroidectomy than after radioiodine therapy. In a recent unrandomised study 30 patients with GD and mild or absent TAO were treated with near-total thyroidectomy and compared with matched controls treated with antithyroid drugs (49). The surgical treatment was not associated with significant effects on the course of TAO after 12 months' follow-up.

Antithyroid drug therapy

Antithyroid drug treatment depresses the autoimmune reactions involved in Graves' hyperthyroidism; this can be demonstrated by a decrease over time in titers of TSH receptor antibodies (50). A similar depression of the autoimmunity (which, in part, seems to involve TSH receptor-related antibodies) involved in Graves' ophthalmopathy would be expected. In accordance with this, only a limited risk (between 0 and 10%) of worsening/activation of TAO associated with antithyroid drug therapy has been demonstrated in prospective studies (9, 14, 51). The problem of medical treatment of Graves' hyperthyroidism, however, is that in 33–50% of the patients a relapse of thyrotoxicosis follows withdrawal of treatment, and therefore physicians often opt for a more radical type of therapy in patients with, e.g. a large goitre, high TRAb levels or high serum T_3 concentrations at start of therapy (52). Prolonging antithyroid drug therapy has never been proven beneficial for prevention/improvement of TAO.

Do glucocorticoids have a protective role on TAO treated by ^{131}I ?

Only one study (14) has evaluated this question. One hundred and forty-five patients with no or only slight ophthalmopathy were treated with 0.4–0.5 mg of prednisone/kg body weight starting 2–3 days after radioiodine therapy and continuing for 1 month before tailing off to zero over a period of 2 months. In none of the patients did TAO worsen (Table 2). Steroids thus completely prevented aggravation of the eye disease. In 25 patients with GD with mild or no signs of TAO undergoing subtotal thyroidectomy, TAO progressed in 6 of 11 patients not receiving glucocorticoids compared with none in the group given glucocorticoids (47).

The question, however, is whether it is reasonable to treat 150 patients prophylactically with a dose of approximately 30 mg of prednisolone for 3 months to avoid development of treatment requiring ophthalmopathy in eight patients.

Discussion

Generally the question of whether the change in degree of ophthalmopathy is a result of the treatment or a result of the spontaneous course of TAO can be raised. Untreated TAO tends to initially progress, stabilize for a period, and eventually remit. It is therefore imperative to use clinically randomized and controlled studies for evaluation of different effects of various treatment regimens. The prospective controlled studies (9, 14) have revealed a higher risk of activation/worsening in TAO during ^{131}I therapy compared with surgery or medical antithyroid treatment, but in none of the studies were the observers blinded to the type of treatment administered.

One of the main problems in evaluating changes in TAO is the difficulty in measuring involvement of thyroid eye disease. The degree of ocular involvement was measured in the majority of the more recent papers according to an ophthalmopathy index based on guidelines for scoring the severity of TAO produced by the American Thyroid Association. It may, however, be more relevant to score activity rather than severity and the lack of precise evaluation of ocular involvement may thus partly explain conflicting results. Another explanation of conflicting results is that in some of the studies patients with severe TAO were excluded and only patients with mild or no TAO included, while in other studies all patients with GD were included. Furthermore, the retrospective feature of most of the studies weakens the results. The study by Tallstedt *et al.* (9) has been confounded by a more frequent occurrence of periods of hypothyroidism after radioiodine as compared with other treatment modalities and the uneven distribution of smokers between treatment groups. However, the study by Bartalena *et al.* (14) has revealed more evidence of the risk of radioiodine therapy in relation to TAO, and this fact has already been impacted in terms of clinical practice in Europe. In a recent survey among European Thyroid Association respondents, 60% altered treatment of GD in cases of eye signs, and of these, 67% avoided ^{131}I in the presence of severe TAO (53).

It would be appropriate to select the subgroup of patients with GD who is at risk of developing/worsening TAO, and several attempts have been made to find predictors for the risk of developing TAO subsequent to the start of therapy for thyrotoxicosis. A meta-analysis of 10 prospective studies showed that lacking presence of TSH receptor antibodies after antithyroid drug treatment of patients with GD reduced the risk of recurrence, but that about 25% of the patients were misclassified (50). Another possible biochemical marker of the immunological pathogenesis of TAO has been suggested Gunji *et al.* (54) who found a close relationship between eye muscle disease and serum antibodies against the flavoprotein subunit of mitochondrial succinate dehydrogenase in patients with GD. As previously mentioned, smoking habits, the function of the thyroid

gland, the dose of radioiodine and the number of ¹³¹I therapies may have an influence. Finally, a possible effect of pretreatment with antithyroid drugs has not been investigated in randomised clinical trials, although it might reduce the amount of antigen released after both ¹³¹I treatment and surgery. Kung *et al.* (12) were unable to demonstrate a higher risk of development or exacerbation of TAO in patients with pre-existing TAO and could not demonstrate a prognostic significance of the presence of TSH receptor antibodies in development of TAO after ¹³¹I treatment. Future research may reveal whether the presence of antibodies against eye muscle antigens and/or eye muscle fibroblasts or preadipocytes can predict an increased risk of development or aggravation of TAO during ¹³¹I therapy.

The precise mechanism by which ¹³¹I causes infiltrative ophthalmopathy is uncertain and details of the immunopathogenesis of TAO is of vital importance to develop eye protective strategies.

Conclusion

Radioiodine worsens TAO in some patients, even though the effect is usually modest. It may therefore be important to recognize patients who may be at a greater risk of worsening ophthalmopathy. It is tempting to suggest the following possible risk factors: pre-existing ophthalmopathy (especially TAO in an active, rather than a static, stage); heavy smoking; more severe thyrotoxicosis; and a history of multiple ¹³¹I therapies. In these patients concomitant corticosteroid administration and early replacement with thyroxine should be considered.

Furthermore, smokers with GD should be recommended to refrain. In patients with already developed active mild or moderate TAO, or at risk of developing TAO, either continuous medical antithyroid treatment or surgical/radioiodine treatment under protection with systemic glucocorticoids may be preferred.

References

- 1 Bahn RS & Heufelder AE. Mechanisms of disease: pathogenesis of Graves' ophthalmopathy. *New England Journal of Medicine* 1993 **329** 1468–1475.
- 2 Bech K. Thyroid antibodies in endocrine ophthalmopathy. *Acta Endocrinologica* 1989 **121** (Suppl 1) 117–122.
- 3 Weetman AP. Eyeing up Graves' ophthalmopathy. *Molecular and Cellular Endocrinology* 1997 **126** 113–116.
- 4 Gunji K, Kubota S, Swanson J, Kiljanski J, Bednarczyk T, Wengrowitz S *et al.* Role of the eye muscles in thyroid eye disease: identification of the principal autoantigens. *Thyroid* 1998 **8** 553–556.
- 5 Natt N & Bahn RS. Cytokines in the evolution of Graves' ophthalmopathy. *Autoimmunity* 1997 **26** 129–136.
- 6 Weetman AP, Cohen S, Gatter KC, Fells P & Shine B. Immunohistochemical analysis of the retrobulbar tissues in Graves' ophthalmopathy. *Clinical and Experimental Immunology* 1989 **75** 222–227.
- 7 Tan GH, Dutton CM & Bahn RS. Interleukin-1 receptor antagonist and soluble interleukin-1 receptor inhibit interleukin-1-induced glycosaminoglycan production in cultured human orbital fibroblasts from patients with Graves' ophthalmopathy. *Journal of Clinical Endocrinology and Metabolism* 1995 **81** 449–452.
- 8 DeGroot LJ, Gorman CA, Pinchera A, Bartalena L, Marcocci C, Wiersinga WM *et al.* Therapeutic controversies. Retro-orbital radiation and radioactive iodide ablation of the thyroid may be good for Graves' ophthalmopathy. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 339–349.
- 9 Tallstedt L, Lundell G, Törring O, Wallin G, Ljunggren J-G, Blomgren H *et al.* Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. *New England Journal of Medicine* 1992 **326** 1733–1738.
- 10 Karlsson FA, Dahlberg PA, Jansson R, Westermarck K & Enoksson P. Importance of TSH receptor activation in the development of severe endocrine ophthalmopathy. *Acta Endocrinologica* 1989 **121** (Suppl 2) 132–141.
- 11 Prummel MF, Wiersinga WM, Mourits MPh, 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.
- 12 Kung AEC, Yau CC & Cheng A. The incidence of ophthalmopathy after radioiodine therapy for Graves' disease: prognostic factors and the role of methimazole. *Journal of Clinical Endocrinology and Metabolism* 1994 **79** 542–546.
- 13 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.
- 14 Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E *et al.* Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *New England Journal of Medicine* 1998 **338** 73–78.
- 15 Prummel MF & Wiersinga WM. Smoking and risk of Graves' disease. *Journal of the American Medical Association* 1993 **269** 479–482.
- 16 Tallstedt L, Lundell G & Taube A. Graves' ophthalmopathy and tobacco smoking. *Acta Endocrinologica* 1993 **129** 147–150.
- 17 Pfeilschifter J & Ziegler R. Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs life-time cigarette consumption. *Clinical Endocrinology* 1996 **45** 477–481.
- 18 Bartalena L, Marcocci C, Tanda ML, Manetti L, Dell'Unto E, Bartolomei MP *et al.* Cigarette smoking and treatment outcomes in Graves' ophthalmopathy. *Annals of Internal Medicine* 1998 **129** 632–635.
- 19 Feldt-Rasmussen U, Bech K, Date J, Petersen PH & Johansen K. A prospective study of the differential changes in serum thyroglobulin and its autoantibodies during propylthiouracil or radioiodine therapy of patients with Graves' disease. *Acta Endocrinologica* 1982 **99** 379–385.
- 20 Jarlov AE, Faber J, Hegedüs L & Hansen JM. Subtle changes in serum thyrotrophin (TSH) and sex-hormone-binding globulin (SHBG) levels during long-term follow-up after radioactive iodine in multinodular non-toxic goitre. *Clinical Endocrinology* 1992 **37** 335–337.
- 21 Nygaard B, Faber J & Hegedüs L. Acute changes in thyroid volume and function following ¹³¹I therapy of multinodular goitre. *Clinical Endocrinology* 1994 **41** 715–718.
- 22 Bech K & Madsen SN. Influence of treatment with radioiodine and propylthiouracil on thyroid stimulating immunoglobulins in Graves' disease. *Clinical Endocrinology* 1980 **13** 417–424.
- 23 Chiovato L, Fiore E, Vitti P, Rocchi R, Rago T, Dokic D *et al.* Outcome of thyroid function in Graves' patients treated with radioiodine: role of thyroid-stimulating and thyrotropin-blocking antibodies and of radioiodine-induced thyroid damage. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 40–46.
- 24 Nygaard B, Knudsen JH, Hegedüs L, Vejle A & Hansen JEM. Thyrotropin receptor antibodies and Graves' disease, a side-effect of ¹³¹I treatment in patients with non-toxic goiter. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 2926–2930.

- 25 Huysmans DAKC, Hermus ARMM, Edelbroek MAL, Tjabbes T, Oostdijk A, Ross HA *et al.* Autoimmune hyperthyroidism occurring late after radioiodine treatment for volume reduction of large multinodular goiters. *Thyroid* 1997 7 535–539.
- 26 Nygaard B, Faber J, Veje A, Hegedüs L & Hansen JM. Transition of nodular toxic goiter to autoimmune hyperthyroidism triggered by ^{131}I therapy. *Thyroid* 1999 9 477–481.
- 27 Bennedbaek FN, Gram J & Hegedüs L. The transition of subacute thyroiditis to Graves' disease as evidenced by diagnostic imaging. *Thyroid* 1996 6 457–459.
- 28 Bartalena L, Bogazzi F, Pecori E & Martino E. Graves' disease occurring after subacute thyroiditis: report of a case and review of the literature. *Thyroid* 1996 6 345–348.
- 29 Monzani F, Del Guerra P, Caraccio N, Casolaro A, Lippolis PV & Goletti O. Appearance of Graves' disease after percutaneous ethanol injection for the treatment of hyperfunctioning thyroid adenoma. *Journal of Endocrinological Investigation* 1997 20 294–298.
- 30 Verde G. Graves' disease after percutaneous ethanol injection for the treatment of autonomous thyroid adenoma. *Journal of Endocrinological Investigation* 1998 21 334–335.
- 31 Bliddal H, Bech K, Feldt-Rasmussen U, Hoier-Madsen M, Thomsen B & Nielsen H. Humoral autoimmune manifestation in subacute thyroiditis. *Allergy* 1985 40 599–604.
- 32 Bech K, Feldt-Rasmussen U, Bliddal H, Date J & Blichert-Toft M. The acute changes in thyroid stimulating immunoglobulins, thyroglobulin and thyroglobulin antibodies following subtotal thyroidectomy. *Clinical Endocrinology* 1982 16 235–242.
- 33 Feldt-Rasmussen U. Serum thyroglobulin and thyroglobulin autoantibodies in thyroid diseases. Pathogenic and diagnostic aspects. *Allergy* 1983 38 369–387.
- 34 Soliman M, Kaplan E, Abdel-Latif A, Scherberg N & DeGroot LJ. Does thyroidectomy, radioactive iodine therapy, or antithyroid drug treatment alter reactivity of patients' T-cells to epitopes of thyrotropin receptor in autoimmune thyroid diseases? *Journal of Clinical Endocrinology and Metabolism* 1995 80 2312–2321.
- 35 Kriss JP, Pleshakov V, Rosenblum AL, Holderness M, Sharp G & Utiger R. Studies on the pathogenesis of the ophthalmopathy of Graves' disease. *Journal of Clinical Endocrinology and Metabolism* 1967 27 582–593.
- 36 Barbosa J, Wong E & Doe RP. Ophthalmopathy of Graves' disease: Outcome after treatment with radioactive iodine, surgery or antithyroid drugs. *Archives of Internal Medicine* 1972 130 111–113.
- 37 Vestergaard H & Laurberg P. Radioiodine and aggravation of Graves' ophthalmopathy. *Lancet* 1989 8653 47.
- 38 Barth A, Probst P & Burgi H. Identification of a subgroup of Graves' disease patients at higher risk for severe ophthalmopathy after radioiodine. *Journal of Endocrinological Investigation* 1991 14 209–212.
- 39 Hamilton RD, Mayberry WE, McConahey WM & Hanson KC. Ophthalmopathy of Graves' disease: A comparison between patients treated surgically and patients treated with radioiodide. *Mayo Clinic Proceedings* 1967 42 812–818.
- 40 Calissendorf BM, Söderström M & Alveryd A. Ophthalmopathy and hyperthyroidism: a comparison between patients receiving different antithyroid treatments. *Acta Ophthalmologica* 1986 64 698–703.
- 41 Sridama V & DeGroot LJ. Treatment of Graves' disease and the course of ophthalmopathy. *American Journal of Medicine* 1989 87 70–73.
- 42 Aranow H & Day RM. Management of thyrotoxicosis in patients with ophthalmopathy: antithyroid regimen determined primarily by ocular manifestations. *Journal of Clinical Endocrinology* 1965 25 1–10.
- 43 Manso PG, Furlanetto RP, Wolosker AMB, Paiva ER, de Abreu MT & Maciel RMB. Prospective and controlled study of ophthalmopathy after radioiodine therapy for Graves' hyperthyroidism. *Thyroid* 1998 8 49–52.
- 44 DeGroot LJ, Manglabruks A & McCormick M. Comparison of RA^{131}I treatment protocols for Graves' disease. *Journal of Endocrinological Investigation* 1990 13 111–118.
- 45 Chiovato L, Santini F, Vitti P, Bendinelli G & Pinchera A. Appearance of thyroid stimulating antibody and Graves' disease after radioiodine therapy for toxic nodular goitre. *Clinical Endocrinology* 1994 40 803–806.
- 46 Nygaard B, Metcalfe RA, Phipps J, Weetman AP & Hegedüs L. Graves' disease and thyroid associated ophthalmopathy triggered by ^{131}I treatment of non-toxic goiter. *Journal of Endocrinological Investigation* 1999 22 481–485.
- 47 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.
- 48 Fernández Sanchez JR, Rosell Pradas J, Carazo Martinez O, Torres Vela E, Escobar Jimenez F, Garbin Fuertes I *et al.* Graves' ophthalmopathy after subtotal thyroidectomy and radioiodine therapy. *British Journal of Surgery* 1993 80 1134–1136.
- 49 Marcocci C, Bruno-Bossio G, Manetti L, Tanda ML, Miccoli P, Iacconi P *et al.* The course of Graves' ophthalmopathy is not influenced by near total thyroidectomy: a case-control study. *Clinical Endocrinology* 1999 51 503–508.
- 50 Feldt-Rasmussen U, Schleusener H & Carayon P. Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long term remission after medical therapy of Graves' disease. *Journal of Clinical Endocrinology and Metabolism* 1994 78 98–102.
- 51 Solem JH, Segard E & Ytteborg J. The course of endocrine ophthalmopathy during antithyroid therapy in a prospective study. *Acta Medica Scandinavica* 1979 205 111–114.
- 52 Feldt-Rasmussen U, Glinoe D & Orgiazzi J. Reassessment of antithyroid drug therapy of Graves' disease. *Annual Review of Medicine* 1993 44 323–334.
- 53 Weetman AP & Wiersinga WM. Current management of thyroid-associated ophthalmopathy in Europe. Results of an international survey. *Clinical Endocrinology* 1998 49 21–28.
- 54 Gunji K, De Bellis A, Kubota S, Swanson J, Wengrowicz S, Cochran B *et al.* Serum antibodies against the flavoprotein subunit of succinate dehydrogenase are sensitive markers of eye muscle autoimmunity in patients with Graves' hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism* 1999 84 1255–1262.
- 55 Vazquez-Chavez C, Nishimura ME, Espinosa SL, Delgado FA & Sainz de Viteri M. Effect of the treatment of hyperthyroidism on the course of exophthalmos. *Revista de Investigacion Clinica* 1992 44 241–247.

Received 5 January 2000

Accepted 3 March 2000