Radioiodine Thyroid Ablation in Graves’ Hyperthyroidism: Merits and Pitfalls

J. F. Nwatsock¹, D. Taieb¹, L. Tessonnier¹, J. Mancini³, F. Dong-A-Zok², O. Mundler¹

¹Service Central de Biophysique et de Médecine Nucléaire, ²Service d’Épidémiologie, CHU de la Timone; 3Service de Médecine Nucléaire, Hôpital Général de Yaoundé; BP: 5408 Yaoundé, Cameroun

Abstract

Ablative approaches using radioiodine are increasingly proposed for the treatment of Graves’ disease (GD) but their ophthalmologic and biological autoimmune responses remain controversial and data concerning clinical and biochemical outcomes are limited. The aim of this study was to evaluate thyroid function, TSH-receptor antibodies (TRAb) and Graves’ ophthalmopathy (GO) occurrence after radioiodine thyroid ablation in GD. We reviewed 162 patients treated for GD by iodine-131 (¹³¹I) with doses ranging from 370 to 740 MBq, adjusted to thyroid uptake and sex, over a 6-year period in a tertiary referral center. Collected data were compared for outcomes, including effectiveness of radioiodine therapy (RIT) as primary endpoint, evolution of TRAb, and occurrence of GO as secondary endpoints. The success rate was 88.3% within the first 6 months after the treatment. The RIT failure was increased in the presence of goiter (adjusted odds ratio = 4.1, 95% confidence interval 1.4–12.0, P = 0.010). The TRAb values regressed with time (r = −0.147; P = 0.042) and patients with a favorable outcome had a lower TRAb value (6.5 ± 16.4 U/L) than those with treatment failure (23.7 ± 24.2 U/L, P < 0.001). At the final status, 48.1% of patients achieved normalization of serum TRAb. GO occurred for the first time in 5 patients (3.7%) who were successfully cured for hyperthyroidism but developed early and prolonged period of hypothyroidism in the context of antithyroid drugs (ATD) intolerance (P = 0.003) and high TRAb level (P = 0.012). On the basis the results of this study we conclude that ablative RIT is effective in eradicating Graves’ hyperthyroidism but may be accompanied by GO occurrence, particularly in patients with early hypothyroidism and high pretreatment TRAb and/or ATD intolerance. In these patients, we recommend an early introduction of LT4 to reduce the duration and the degree of the radioiodine-induced hypothyroidism.

Keywords: Autoimmunity, Graves’ disease, ophthalmopathy, radioiodine therapy

Introduction

Graves’ disease (GD) is the most common cause of hyperthyroidism. This recurrent autoimmune disease combines in variable proportions—hyperthyroidism, goiter, and Graves’ ophthalmopathy (GO). Hyperthyroidism and goiter are related to an aberrant stimulation of thyrotropin receptors (TSHR) by stimulating TSHR autoantibodies (TRAb). The mechanism involved in GO is more complex and not clearly established.[1,2]

Treatment options include antithyroid drugs (ATD), thyroid surgery, and radioiodine therapy (RIT).[3,4] The first choice of treatment differs from country to country and RIT can be administered either as first-line treatment or if the hyperthyroidism is not controlled or recurs after ATD treatment or thyroid surgery.[5-7] Several factors have been associated with increased risk of radioiodine therapy failure, such as low dose regimen, low thyroid uptake, male gender, presence of goiter, and severity of hyperthyroidism.[8-13] The choice of the dose planning (low vs high doses) for RIT mainly depends on the therapeutic goals. Recent studies
suggesst delivering high doses to avoid persistent hyperthyroidism and reduce recurrences. The optimal approach for delivering high doses is still debated and could include administration of a fixed high $^{131}$I activity or adjusted activities (adjusted to radioiodine uptake, sex, and/or thyroid volume) to deliver a target dose in the range of 200 Gy. [14-16]

Radioiodine therapy is a relatively safe procedure with a high cost-effectiveness ratio but may be associated with an occasional exacerbation of autoimmunity and GO. [13,17-20] Our large retrospective study aims to evaluate thyroid function, TRAb course, and GO occurrence after radioiodine thyroid ablation for GD.

**Patients and Methods**

**Study design and patients**

We carried out a retrospective study of patients treated for GD by radioiodine over a period of 6 years (from February 2004 to February 2010) in the Nuclear Medicine Department of La Timone Hospital. We reviewed the data of 249 patients with diagnosis of GD who received radioiodine therapy during the study period. Among these patients, 162 (65.1%) who had a complete clinical and biological followup after 6 months were eligible for the study, irrespective of age, presumed type of treatment, and associated conditions. The diagnosis of GD was underpinned by the endocrinologists based on clinical, biochemical, and imaging findings. GO was defined and clinically graduated according to the classification of Werner. [21,22] Goiter was defined by a thyroid volume > 30 mL using neck ultrasound according to the classical ellipsoidal formula. TSH, FT$_4$, and FT$_3$ were determined before RIT and every month until the occurrence of radioiodine-induced hypothyroidism. At baseline, TRAb values were assessed using a second-generation assay with a lower functional sensitivity of 0.9 UI/L. Hormonal status and TRAb were also assessed at the time of the data collection, corresponding to final disease status for patients. Hyperthyroidism, hypothyroidism, and euthyroidism were defined as TSH$_{US}$ < 0.3 mU/L, TSH$_{US}$ > 5 mU/L (without ATD) and TSH$_{US}$ from 0.3 to 5 mU/L (without ATD), respectively. Ablation success was defined as the achievement of hypothyroidism and/or euthyroidism in patients without ATD.

**Treatment protocol**

Estimation of 24-h RIT uptake using a gamma-counter (Europrobe®) equipped with a high-energy probe was performed in all patients (3.7 MBq of $^{131}$I). Female patients with uptake > 40% received ablative activity of 370 MBq. Those with uptake between 10% and 40% received 555 MBq, whereas patients with uptake < 10% received 740 MBq. In case of previous thyroid surgery, a fixed activity of 370 MBq was administered; and all patients with recurrences after previous RIT received 740 MBq. Patients on ATD stopped it at least 5 days before RIT. In patients with GO, corticoids were prescribed (prednisone 0.5 mg/kg starting from 1 week prior to 4 weeks after RIT). Comorbidities were treated according to protocols introduced by specialized physicians. Good oral water intake, hygiene, and radiation protection rules were recommended when patients were discharged. The first followup evaluation was done after 4 weeks of radioiodine therapy.

**Statistical analysis**

The results are expressed as frequencies and means ± standard deviation. Comparison of continuous variables was done using Mann–Whitney $U$ test and Kruskal–Wallis test. Associations between variables and comparison of proportions were done using Pearson’s Chi-square test and Fisher’s exact test. After univariate and multivariate analyses, a logistic regression model was conducted to study factors independently associated with treatment failure. Evolution of TRAb was described using linear regression and Pearson’s correlation coefficient. $P$ values < 0.05 were considered significant (SPSS® 17.0 software for Windows®).

**Results**

**Characteristics of the patients on admission**

The age of the study population ranged from 22 to 89 years with mean age of 58.3 ± 14.3 years. The male to female ratio was 1/4.4. The RIT was indicated for recurrent or persistent hyperthyroidism (after at least one cycle of ATD) in 148 patients (91.4%) and for ATD intolerance in 14 patients (8.6%). The initial prevalence of GO in our population was 16.7% (27 patients). The mean time between the diagnosis and radioiodine therapy was 56.6±73.0 months (2–384). Sixty-nine patients (42.6%) had goiter. Biologically, the mean values on admission were TSHus 0.94±2.67 mU/L; FT$_4$ 22.23±12.92 pmol/L and FT$_3$ 13.20±4.43 pmol/L. TRAb were significantly present in 134 patients (82.7%). These variables did not show significant differences concerning administered radioiodine activity. The mean followup duration was 29.44±15.06 (3–62) months.

**Effectiveness of $^{131}$I-radioiodine on thyroid function**

As shown in Table 1, 143 patients (88.3%) were hypothyroid or euthyroid within the first 6 months. After 6 months, 108/114 patients remained hypothyroid and 6/114 switched to euthyroidism (4 cases) or recurrent hyperthyroidism (2 cases). Among 29 euthyroid patients, 14 switched to hypothyroidism (13 cases) or recurrent hyperthyroidism (1 case). Within the persistent
hyperthyroidism subgroup, 18/19 patients were retreated with radical therapeutic approaches (17 RIT, 1 thyroidectomy) and were excluded from the analysis of thyroid outcomes after 6 months and 1/19 became euthyroid later without any additional treatment. The global failure of RIT within the first 6 months (11.7%) was irrespective of \(^{131}I\) activity administered \((P = 0.72)\) [Table 1]. After univariate and multivariate tests including age, \(^{131}I\) activity, sex-ratio, time to diagnosis, presence of goiter, TSH, FT\(_4\), FT\(_3\), and TRAb values, overall analysis showed that effectiveness decreased in presence of goiter \((P = 0.010)\) [Table 2].

**Evolution of TRAb**

Before \(^{131}I\) therapy, the mean TRAb value was 7.8±9.7 U/L. Figure 1 shows that TRAb values regressed with time \((r = 0.147; P = 0.042)\). The patients with a favorable outcome had, at the time of the data collection, a lower TRAb value (6.5±16.4 U/L) than those with treatment failure (23.7 ± 24.2 U/L, \(P < 0.001\)). Seventy-eight patients (48.1%) achieved normalization of serum TRAb at the time of data collection.

**The course of Graves’ ophtalmopathy**

Before RIT, 27 patients (16.7%) had clinical manifestations of GO classified from 1 to 4 using Werner’s classification and received corticoid treatment. During the followup, GO occurred in 5 patients (3.7% of patients without initial ophtalmopathy) and worsened in 2 patients (7.4% of patients with initial ophtalmopathy) despite the use of corticoids. The characteristics of patients with increased GO after RIT are detailed in Table 3. Interestingly, all patients with occurrence or worsening of GO were successfully cured of hyperthyroidism but developed severe, early and prolonged period of hypothyroidism. The occurrence of GO was statistically related to the ATD intolerance \((P = 0.003)\) and to the presence of high TRAb level \((P = 0.012)\) before the treatment [Table 4].

**Discussion**

In the present study, we found that adjusted ablative RIT was effective in eradicating Graves’ hyperthyroidism but

---

**Table 1: Effectiveness of administered activities**

| \(\leq 6\) months post-RIT (n=162) | Hypo | Eu | Hyper | \(P\) |
|----------------------------------|------|----|--------|-----|
| 370 MBq (n=22)                  | 12 (54.5%) | 7 (31.8%) | 3 (13.7%) | 0.72 |
| 555 MBq (n=97)                  | 78 (80.4%) | 9 (9.3%) | 10 (10.3%) |    |
| 740 MBq (n=43)                  | 24 (55.8%) | 13 (30.2%) | 6 (14.0%) |    |
| Total                           | 114 (70.4%) | 29 (17.9%) | 19 (11.7%) |    |

| \(> 6\) months post-RIT (n=144) | Hypo | Eu | Hyper | \(P\) |
|---------------------------------|------|----|--------|-----|
| 370 MBq (n=20)                 | 13 (65.0%) | 6 (30.0%) | 1 (5.0%) | 0.82 |
| 555 MBq (n=87)                 | 79 (90.8%) | 7 (8.0%) | 1 (1.2%) |    |
| 740 MBq (n=37)                 | 29 (78.4%) | 7 (18.9%) | 1 (2.7%) |    |
| Total                          | 121 (84.0%) | 20 (13.9%) | 3 (2.1%) |    |

143 patients were hypothyroid or euthyroid during the 6 first months. After 6 months, 18 patients with persistent hyperthyroidism were retreated with RIT or surgery and were not included to the analysis of thyroid outcomes. The success of treatment was not respective of \(^{131}I\) activities.

**Table 2: Analysis of treatment failure at ≤6months post-\(^{131}I\)**

| Variables                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
| \(^{131}I\) activity (MBq)       | Success             | Failure               | \(P\)      | 95% confidence interval | Adjusted odds ratio | \(P\) |
| 57.8±11.4 (162) | 58.2±124.1 | 0.885 | 0.123-2.602 | 0.567 | 0.465 |
| Age (years)                     | 58.1±14.3 (162) | 58.8±14.9 | 0.881 | 0.966-1.044 | 1.004 | 0.840 |
| M-to-F ratio (ratio)            | 0.22 (162) | 0.25 | 0.769 | 0.220-3.800 | 0.914 | 0.902 |
| Time to Dg (months)             | 64.2±18.2 (162) | 45.3±50.4 | 0.998 | 0.991-1.006 | 0.999 | 0.717 |
| Presence of Goiter (%)          | 39.4 (162) | 70.00 | 0.009 | 1.395-11.990 | 4.090 | 0.010 |
| TSH values (mUI/l)              | 1.03±2.82 (162) | 0.37±0.75 | 0.948 | 0.404-1.217 | 0.701 | 0.208 |
| FT4 values (pmol/l)             | 22.53±12.55 (162) | 20.27±15.58 | 0.285 | 0.924-1.027 | 0.974 | 0.333 |
| FT3 (pmol/l)                    | 13.77±47.13 (162) | 9.23±9.88 | 0.411 | 0.939-1.054 | 0.995 | 0.864 |
| Pretreatment TRAb (UI/l)        | 8.02±9.73 (162) | 7.02±9.62 | 0.628 | 0.926-1.044 | 0.983 | 0.578 |

Univariate and multivariate analyses show that effectiveness of RIT decreased in presence of goiter.
Table 3: Characteristics of patients with occurred or worsened GO after RIT (n=7)

| Patients | Group | Age (years) | Sex | Time to Dg (months) | TRAb | Pre-treatment | 131I activity | TSH | FT4 | FT3 | Hypo at Duration |
|----------|-------|-------------|-----|---------------------|------|--------------|--------------|-----|-----|-----|-----------------|
|          | Occurrence | 44 | F | 3 | ABD intolerance | 15.7 | No | 555 | <0.05 | 32.9 | 13.47 | 1 month | 2 months |
|          | Occurrence | 49 | F | 420 | Recurrence | 12 | 131I | 555 | 3.3 | 2036 | 13.8 | 1.5 month | 3 months |
|          | Occurrence | 56 | F | 12 | Persistence | 13 | ABD | 740 | <0.05 | 7.1 | 3.9 | 1 month | 1 month |
|          | Occurrence | 41 | F | 10 | ABD intolerance | 13 | No | 370 | <0.05 | 12.8 | 822 | 2 months | 1.5 month |
|          | Occurrence | 55 | M | 3 | ABD intolerance | 10 | No | 740 | <0.05 | 21.0 | 17.5 | 1 month | 4 months |
|          | Worsening | 65 | M | 3 | ABD intolerance | 3.7 | No | 740 | <0.05 | 14.6 | 4.81 | 1 month | 4 months |
|          | Worsening | 71 | F | 72 | Recurrence | 19.6 | ABD | 555 | <0.05 | 12.59 | 32.3 | 2 months | 3 months |

Table 4: Analysis of parameters influencing occurrence of GO (n=135)

| Parameters | Absence of GO (n=130) | Occurrence of GO (n=5) | P values |
|------------|-----------------------|------------------------|----------|
| Age (years) | 59.2±14.2 | 49.0±6.6 | 0.064 |
| M-to-F ratio | 0.22 | 0.25 | 0.548 |
| Time to Dg (months) | 59.2±77.4 | 109.0±207.3 | 0.398 |
| ABD intolerance (%) | 9.8 | 80.0 | 0.003 |
| Pretreatment TRAb (UI/l) | 7.6±9.9 | 12.7±2.0 | 0.012 |
| Pre-131I TSH (mUI/l) | 1.0±2.8 | 0.6±1.4 | 0.143 |
| Pre-131I FT4 (pmol/l) | 22.4±13.6 | 18.8±9.7 | 0.692 |
| Pre-131I FT3 (pmol/l) | 13.7±48.9 | 11.2±5.2 | 0.308 |

Table 3: Characteristics of patients with occurred or worsened GO after RIT (n=7)

was associated with 3.7% of GO occurrence. According to previous studies using ablative approaches,\[14-16\] we found a high rate of radioiodine-induced hypothyroidism. The presence of goiter was predictive of treatment failure. In most cases, hypothyroidism occurred within the first 6 months and only few patients developed hypothyroidism after 6 months. However, delayed hypothyroidism should have been underestimated in our study because 18/19 patients with persistent hyperthyroidism were submitted to an additional radical treatment at 6 months post-initial RIT. Contrastingly to calculated low doses regimen, the adjusted ablative approach provides more ability to predict permanent hypothyroidism but one third of patients developed a severe hypothyroidism at 1 month post-RIT. An earlier introduction of L-thyroxin treatment should reduce the overall period of hypothyroidism.

A transient rise in serum TRAb has been reported immediately after 131I therapy, followed by a period of decrement.\[28\] It has been demonstrated that remission of TRAb after RIT was less common than following surgery or ATD.\[19\] In our study, 48.1% of patients achieved normalization of serum TRAb. As described in literature, patients with persistent hyperthyroidism had significantly higher rates of TRAb than other patients.

We found that ablative RIT was associated with 3.7% of GO occurrence. The course of GO after RIT remains controversial.\[3,13,24-28\] The initial prevalence of GO was low in our population (16.7%) compared with the usual prevalence of clinically significant GO, which may be present in over 50% of Graves’ disease patients.\[29\] The low prevalence in our population is rather reflective of patient selection for radioiodine RIT in our setting.

The potential role of immune storm following RIT is not clearly understood. Some authors recommend introduction of a corticosteroid prophylactic cover in patients with GO. However, the occurrence or worsening of GO after radioiodine therapy should be more related to radioiodine-induced hypothyroidism.\[18\] Recently, Perros et al. found that RIT was not associated with deterioration of GO in patients with minimally active eye disease when postradioiodine hypothyroidism is prevented and without use of corticoids.\[30\] In our study, patients with occurrence or progression of GO developed an early (1–2 months after radioiodine) and prolonged (1–4 months) hypothyroid period. We also found that ATD intolerance and pre-131I high TRAb were associated with GO occurrence.

## Conclusion

Ablative radioiodine therapy with adjusted activities is effective in eradicating Graves’ hyperthyroidism. But it may be accompanied by a high rate of GO occurrence if hypothyroidism is not prevented. We recommend as other authors to introduce thyroxin supplementation from 15th day onward postradioiodine therapy, particularly in patients with high titers of radioiodine and/or ATD intolerance.

## References

1. Eckstein AK, Plicht M, Lax H, Hirche H, Quadbeck B, Mann K, et al. Clinical results of anti-inflammatory therapy in Graves’ ophthalmopathy and association with thyroidal autoantibodies. Clin Endocrinol (Oxf) 2004;61:612-8.
2. Gerding MN, Van Der Meer JW, Broenink M, Bakker O, Wiersinga WM, Prummel MF. Association of thyrotropin receptor antibodies with the clinical features of Graves’ ophthalmopathy. Clin Endocrinol (Oxf) 2000;52:267-71.
3. Leech NJ, Dayan CM. Controversies in the management of Graves' disease. Clin Endocrinol (Oxf) 1998;49:273-80.
4. Shapiro B. Optimization of radiiodine therapy of thyrotoxicosis: what have we learned after 50 years? J Nucl Med 1993;34:1638-41.
5. Glinoer D, Hesch D, Lagasse R, Laurberg P. The management of hyperthyroidism due to Graves' disease in Europe in 1986: Results of an international survey. Acta Endocrinol Suppl (Copenhagen) 1987;285:3-23.
6. Nagayama Y, Izumi M, Nagataki S. The management of hyperthyroidism due to Graves' disease in Japan in 1988. The Japan Thyroid Association. Endocrinol Jpn 1989;36:299-314.
7. Solomon B, Glinoer D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. J Clin Endocrinol Metab 1990;70:1518-24.
8. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism-prognostic factors for outcome. J Clin Endocrinol Metab 2001;86:3611-7.
9. Catargi B, Leprat F, Guyot M, Valli N, Ducassou D, Tabarin A. Radioiodine treatment of hyperthyroidism: prognostic factors for outcome. J Clin Endocrinol Metab 1999;84:117-21.
10. De Bruin TW, Croon CD, De Klerk JM, Van Isselt JW. Standardized radiodioidine therapy of Graves' disease: Analysis of the delivered dose and of other possible factors affecting outcome. Eur J Endocrinol 1999;141:117-21.
11. De Bruin TW, Croon CD, De Klerk JM, Van Isselt JW. Standardized radiodioidine therapy in Graves' disease: The persistent effect of thyroid weight and radiodiiodine uptake on outcome. J Intern Med 1994;236:507-13.
12. Howarth D, Epstein M, Lan L, Tan P, Booker J. Determination of the optimal minimum radiiodine dose in patients with Graves' disease: A clinical outcome study. Eur J Nucl Med 2001;28:1489-95.
13. Nordyke RA, Gilbert FJ Jr. Optimal iodine-131 dose for eliminating hyperthyroidism in Graves' disease. J Nucl Med 1991;32:411-6.
14. Alexander EK, Larsen PR. High dose of 131I therapy for the treatment of hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 2002;87:1073-7.
15. Horacek J, Franklyn JA. Radioiodine treatment of Graves' hyperthyroidism. J Clin Endocrinol Metab 2003;88(12):611-3.
16. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radiiodine doses in Graves' hyperthyroidism. J Clin Endocrinol Metab 2003;88:978-83.
17. Chiovato L, Fiore E, Vitti P, Rocchi R, Rago T, Dokic D, et al. Outcome of thyroid function in Graves' patients treated with radiodioidine: Role of thyroid-stimulating and thyrotopin-blocking antibodies and of radiodioidine-induced thyroid damage. J Clin Endocrinol Metab 1998;83:40-6.
18. De Groot 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. J Clin Endocrinol Metab 1995;80:339-40.
19. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Torring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: A 5-year prospective randomized study. Eur J Endocrinol 2008;158:69-75.
20. Sridama V, De Groot LJ. Treatment of Graves' disease and the course of ophthalmopathy. Am J Med 1989;87:70-3.
21. Werner SC. Classification of the eye changes of Graves' disease. Am J Ophthalmol 1969:68:646-8.
22. Werner SC. Modification of the classification of the eye changes of Graves' disease. Am J Ophthalmol 1977;83:725-7.
23. Atkinson S, McGregor AM, Kendall-Taylor P, Peterson MM, Smith BR. Effect of radioiodine on stimulated activity of Graves' immunoglobulins. Clin Endocrinol (Oxf) 1982;16:537-43.
24. 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. N Engl J Med 1998;338:73-8.
25. Bonnema SJ, Bartalena L, Toft AD, Hedegus L. Controversies in radioiodine therapy: Relation to ophthalmopathy, the possible radioprotective effect of antithyroid drugs, and use in large goitres. Eur J Endocrinol 2002;147:1-11.
26. Dickinson AJ, Perros P. Controversies in the clinical evaluation of active thyroid-associated orbitopathy: use of a detailed protocol with comparative photographs for objective assessment. Clin Endocrinol (Oxf) 2001;55:283-303.
27. Tallstedt L, Lundell G, Blomgren H, Bring J. Does early administration of thyroxine reduce the development of Graves' ophthalmopathy after radioiodine treatment? Eur J Endocrinol 1994;130:494-7.
28. 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. Clin Endocrinol (Oxf) 1999;51:503-8.
29. Jacobson DH, Gorman CA. Endocrine ophthalmopathy: current ideas concerning etiology, pathogenesis, and treatment. Endocr Rev 1984;3:200-20.
30. Perros P, Kendall-Taylor P, Neoh C, Frewin S, Dickinson J. A prospective study of the effects of radioiodine therapy for hyperthyroidism in patients with minimally active graves' ophthalmopathy. J Clin Endocrinol Metab 2005;90:5321-3.