Does early administration of thyroxine reduce the development of
Graves’ ophthalmopathy after radiiodine treatment?

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The roles of thyroid hormones and thyrotropin (TSH) in the development of Graves’ ophthalmopathy are not clear. Some studies suggest a protective effect of thyroid hormones on experimental exophthalmos and an adverse effect of increased TSH levels. In September 1988 we introduced early thyroxine (T4) administration after 131I therapy for hyperthyroidism caused by Graves’ disease. We carried out a retrospective study of records from all patients with this disease treated with 131I for 4 years. During the first 2 years 248 patients were treated (group A). They received T4 when the serum concentration of TSH and/or T3 indicated hypothyroidism. During the next 2 years 244 patients were treated (group B). They were all given 0.05 mg of T4 daily, starting 2 weeks after therapy, and 0.1 mg after a further 2 weeks. With a follow-up of 18 months, 45 patients (18%) in group A and 27 patients (11%) in group B developed or deteriorated in a already present ophthalmopathy (p = 0.03, relative risk = 1.64, 95% confidence interval = 1.05–2.55). Twenty-six patients in group A required specific therapy for the ophthalmopathy (e.g. antithyroid drugs, steroids, etc.) compared to 11 patients in group B (p = 0.02, relative risk = 2.33; 95% confidence interval = 1.18–4.60). Our results suggest that early administration of T4 after 131I therapy reduces the occurrence of Graves’ ophthalmopathy.

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Radiiodine therapy is a common form of treatment for hyperthyroidism caused by Graves’ disease (1, 2). It has few complications, it can be given on an outpatient basis and it is convenient for the patient. On the other hand, a recent study has shown that the occurrence of Graves’ ophthalmopathy is higher in patients following treatment with 131I compared to patients treated with an antithyroid drug or thyroidectomy (3).

The etiology of Graves’ ophthalmopathy is still unknown. The main target of the orbital inflammation seems to be the extracocular muscles, where infiltrating inflammatory cells in the interstitial tissue have been detected (4–7). The cause of this inflammation is under debate, but there is evidence that autoimmune mechanisms are involved (8). Earlier studies focused on the role of thyrotropin (TSH). Tengroth showed that TSH, injected in thyroidectomized guinea pigs, produced exophthalmos and that thyroxine (T4) was able to prevent this reaction (9). It has been demonstrated also that, in man, the development of Graves’ ophthalmopathy is most frequently seen in the hypothyroid state that may follow therapy (10–12).

The possible protective effect of T4 and the possible adverse effect of increased TSH levels on the development of exophthalmos led us to change the routine of T4 administration after 131I therapy. In this study we have compared retrospectively the development or worsening of Graves’ ophthalmopathy between two groups of patients treated with 131I for hyperthyroidism caused by Graves’ disease. The main difference between the groups is that T4 was given “prophylactically” as early as 2 weeks after isotope treatment in one of the patient groups, whereas in the other, T4 was given when the serum concentration of T4 and/or TSH indicated hypothyroidism.

Materials and methods

Records from all patients treated with 131I at Radiumhemmet, Karolinska Hospital for hyperthyroidism caused by Graves’ disease from 1 September 1986 until 31 August 1990 were examined retrospectively. Graves’ disease was diagnosed by raised levels of serum T3 and/or T4, radiiodine tracer tests and thyroid scintigraphy. Altogether, 745 patients were treated: 367 during the first 2 years and 378 during the next 2 years. All patients who had been treated previously for hyperthyroidism were excluded, leaving 248 patients treated during the first 2 years (group A) and 244 treated during the next 2 years (group B).

Patients in group A were examined at 6 and 10 weeks after the radiotherapy. If they were still hyperthyroid at 10 weeks and the 131I uptake permitted, then further 131I therapy was given. When
the patients were euthyroid, they were seen every 3 months until the serum concentration of TSH and/or T₄ indicated hypothyroidism (TSH > 4.5 mU/l, T₄ < 7.5 nmol/l), at which time T₄ was given.

All patients in group B were given 0.05 mg of T₄ daily, starting 2 weeks after ¹³¹I therapy, and then after another 2 weeks the dose was raised to 0.1 mg daily. Also in this group, all patients were seen 6 and 10 weeks after therapy and if they were still hyperthyroid at 10 weeks then additional radiotherapy was given, based on the same principles as in group A, in most cases without withdrawing T₄ therapy. In 131 patients (54%) the T₄ dose was later increased from 0.1 mg.

The therapeutic dose of ¹³¹I, which aimed at exposing the thyroid to 120 Gy, was calculated by taking into account the size of the organ, the 24-h ¹³¹I uptake and the effective half-life of the isotope in the thyroid (13). The size of the thyroid was estimated on the basis of palpation and thyroid scintigraphy.

The two patient groups are comparable regarding the recorded parameters except for the size of the thyroid and the size of the first dose of ¹³¹I administered (Table 1).

The large majority of the patients were treated and followed by two physicians (GL and HB). The presence or absence of Graves’ ophthalmopathy was noted in the records. All the records were examined retrospectively by an ophthalmologist (LT). The patients were classified as either having infiltrative ophthalmopathy, i.e. Werner class II–VI, or not (14). If there was an evidence of increase in soft-tissue involvement, a significant increase in Hertel readings (≥ 3 mm), an increase in diplopia or a decrease in visual acuity, patients were considered as having a worsening of the ophthalmopathy. Likewise, patients who changed from a lower grade to a higher grade of Werner class were considered as having deteriorated. Those with infiltrative ophthalmopathy were subdivided further into those who received specific therapy for the ophthalmopathy and those who did not. Patients whose eye disease did not regress despite an increase of the T₄ dose were treated with glucocorticoids, external retrobulbar radiotherapy, orbital decompression, thyrostatic drugs or two or more of these modalities combined.

The observation period for each group was 18 months.

**Statistical analysis**

The hypothesis that there were no differences between the two groups regarding the occurrence of ophthalmopathy was tested by Fisher’s exact test. Other tests used were the t-test and the chi-squared test. When searching for prognostic factors we applied logistic regression analysis, with the outcome variable defined as the development or worsening of ophthalmopathy.

**Results**

Thirty-seven patients (15%) in group A without ophthalmopathy prior to treatment developed ophthalmopathy after treatment, compared to 23 patients (9%) in group B. Eight patients (3%) in group A and four (2%) in group B deteriorated in an already present ophthalmopathy. Taken together, 45 patients (18%) in group A and 27 (11%) in group B developed ophthalmopathy or worsened in an already present ophthalmopathy (p = 0.04, relative risk = 1.64; 95% confidence interval = 1.05–2.55). Patients in group A had an average increase in Hertel readings of 3.5 mm, compared to 3.2 mm in group B (p > 0.5). Data on the degree of ophthalmopathy are shown in Table 2.

In an attempt to estimate the severity of the ophthalmopathy, the number of patients in both groups who required specific therapy were registered. Twenty-six patients in group A and 11 patients in group B were given such therapy because of progressive eye changes, despite an increase of the T₄ medication (P = 0.02, relative risk = 2.33; 95% confidence interval = 1.18–4.60). Twenty-three of the 26 patients in group A were given antithyroid drugs because of post-treatment ophthalmopathy and eight also were given

<table>
<thead>
<tr>
<th>Table 1. Clinical and demographic characteristics of patients with hyperthyroidism caused by Graves’ disease.*</th>
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<tbody>
<tr>
<td><strong>Group A</strong></td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Percentage of men</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Pretreatment serum T₄ (nmol/l)</td>
</tr>
<tr>
<td>Pretreatment serum T₃ (nmol/l)</td>
</tr>
<tr>
<td>Size of thyroid</td>
</tr>
<tr>
<td>&lt; 30 g, no. (%)</td>
</tr>
<tr>
<td>30–59 g, no. (%)</td>
</tr>
<tr>
<td>≥ 60 g, no. (%)</td>
</tr>
<tr>
<td>First ¹³¹I dose (MBq)</td>
</tr>
<tr>
<td>Number of ¹³¹I doses</td>
</tr>
</tbody>
</table>

* Values are means ± sp.
glucocorticoids, six also were given glucocorticoids and retrobulbar radiation and three also had an orbital decompression. One patient received retrobulbar radiation only. In group B, ten patients were given antithyroid drugs and six also received glucocorticoids, two also were given glucocorticoids together with retrobulbar radiation and one also had an orbital decompression.

Other possible predictive factors for development or worsening of ophthalmopathy were sought by means of univariate analysis (Table 3) and a series of logistic regression analyses. Apart from the different principles for T4 therapy, the variable of importance was the pretreatment serum concentration of T3, which was higher in those patients who developed ophthalmopathy or in those whose ophthalmopathy worsened (p = 0.04).

Fifty-four patients (22%) in group A received more than one radioiodine treatment because of persistent or recurrent hyperthyroidism, compared to 44 patients (18%) in group B. All but 22 patients in group A became hypothyroid during the observation period and were substituted with T4.

Two patients in group B stopped their T4 medication because of tachycardia.

Discussion
The traditional way of substituting patients with T4 after 131I therapy for hyperthyroidism caused by Graves' disease at Radiumhemmet and, we guess, at most institutions, is to start the therapy when the serum concentration of TSH and/or T4 indicates hypothyroidism. From September 1988 we changed this routine at Radiumhemmet and started T4 therapy in all patients 2 weeks after 131I therapy. The reason for this was the early observations that T4 could prevent the development of exophthalmos in experimental studies (9) and reports that an increased TSH level was linked positively to the development of ophthalmopathy (10–12).

In this study we found a significant difference in frequency of infiltrative Graves' ophthalmopathy between the two groups of patients and we found also a significant difference between the groups regarding the severity of ophthalmopathy, i.e. the number of patients requiring specific treatment. This is a retrospective study and data on the patients' eye changes were collected from patient records. Patients complaining of irritation and a gritty sensation in the eyes, in combination with the presence of eye lid edema, chemosis and redness of the eyes, were classified as having ophthalmopathy. Thus, patients with minor changes also were included in the group that deteriorated. After having changed the routines for T4 administration, one can assume that we were even more observant of the presence of ophthalmopathy. Therefore, if this study is biased, one would expect more cases of ophthalmopathy in group B. However, the occurrence of severe ophthalmopathy was significantly higher in group A. The guidelines for specific treatment of ophthalmopathy were the same during both periods.

The mechanisms for this protective effect of early administration of T4 are unclear. Karlsson et al. (12) observed that many of their patients with severe ophthalmopathy had post-therapy hypothyroidism and high levels of thyrotropin receptor antibodies and proposed that the elevated TSH levels could promote a pathogenetic signal in the thyroid. In our study, patients in group A with worsening or development or ophthalmopathy did not have significantly higher maximum serum concentrations of TSH than those who did not experience ophthalmopathy (data not shown). This is in agreement with our findings in a previous study of radioiodine-treated patients with Graves' disease (3). Hashizume et al. (15) showed that the administration of T4 during antithyroid drug treatment decreased the production of thyrotropin receptor antibodies and speculated that T4 might act directly on the B lymphocytes or maybe directly inhibit the production of antigenic substances by the thyroid.

Table 2. Patients who developed ophthalmopathy or deteriorated in an already present ophthalmopathy in each group.*

<table>
<thead>
<tr>
<th>Soft-tissue involvement</th>
<th>Increase of ≥ 3 in Hertel readings</th>
<th>Diplopia</th>
<th>Optic nerve damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>13</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Group B</td>
<td>7</td>
<td>12</td>
<td>15</td>
</tr>
</tbody>
</table>

*The values indicate the most pronounced degree of ophthalmopathy.

Table 3. All patients with Graves' disease divided according to the course of Graves' ophthalmopathy (GO).*

<table>
<thead>
<tr>
<th>Patients with development or worsening of GO</th>
<th>Patients without GO or improvement of GO</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>72</td>
<td>420</td>
</tr>
<tr>
<td>Percentage of men</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Age at treatment (years)</td>
<td>57 ± 11</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>Pretreatment serum T3 (nmol/l)</td>
<td>4.8 ± 1.6</td>
<td>4.4 ± 1.7</td>
</tr>
<tr>
<td>Pretreatment serum T4 (nmol/l)</td>
<td>209 ± 44</td>
<td>197 ± 49</td>
</tr>
</tbody>
</table>

*Values are means ±sd.
There are also recent data suggesting that the TSH receptor can be expressed in orbital tissue (16, 17).

In this study we could confirm the finding from another study (3) that patients with high serum concentrations of T3 prior to therapy have a greater risk of developing ophthalmopathy.

The hazard of starting T4 therapy as early as 2 weeks after 131I treatment was negligible. At this stage the patients were still hyperthyroid, but the addition of 0.05 mg of T4 daily caused no major problems. Only two patients stopped their T4 medication within the first 10 weeks because of tachycardia. No other adverse effects were seen.

There were nine patients during the first 2 years (group A) and 17 during the next 2 years (group B) who were pretreated with antithyroid drugs prior to 131I treatment. These patients were not included in this study. All were elderly with high serum T3 and T4 concentrations who were considered to be at risk for general complications if they were given 131I without reducing the thyroid activity. If these patients are included in the calculations, the degrees of significance are not changed. Thus, we do not believe the fact that more patients were pretreated with antithyroid drugs during the second 2 years could affect our results.

The two groups were comparable except for thyroid size and the 131I dose given. We do not believe that these differences affect the results of the study. There was no difference in thyroid size between patients who developed or deteriorated in a pretherapy ophthalmopathy and those without ophthalmopathy (data not shown). The 131I dose given is based on the effective half-life of 131I and the thyroid size, which fully explains the higher doses administered in group B.

In conclusion, the results of this retrospective study may suggest that early administration of T4 after 131I treatment reduces the occurrence of Graves' ophthalmopathy. We now, as a routine measure, start T4 therapy 2 weeks after the 131I therapy in all patients with hyperthyroidism caused by Graves' disease.

References


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