Abstract

Objective: Radioiodine ($^{131}$I) 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 $^{131}$I 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.

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)-1α 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-1α, 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 ($^{131}$I) has been used to obtain euthyroidism; however, during the past 10 years an $^{131}$I 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 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...
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 $^{131}$I therapies has also been associated with worsening of ophthalmopathy (44).

In patients treated with $^{131}$I 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

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**Table 1** Influence of $^{131}$I treatment on TAO compared with other treatment modalities in retrospective studies.

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

**Table 2** Influence of $^{131}$I treatment on TAO compared with other treatment modalities in two open randomized studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Activation/worsening (%)</th>
<th>95% c.l.</th>
<th>n</th>
<th>Prophylactic $T_4$ substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tallstedt et al. 1992 (9)</td>
<td>Medical antithyroid drug</td>
<td>10</td>
<td>3–25</td>
<td>38</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Surgery (subtotal thyroidectomy)</td>
<td>16</td>
<td>6–32</td>
<td>37</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33</td>
<td>19–50</td>
<td>39</td>
<td>–</td>
</tr>
<tr>
<td>Follow-up: 24 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bartalena et al. 1998 (14)</td>
<td>Medical antithyroid drug</td>
<td>3</td>
<td>1–7</td>
<td>148</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>$^{131}$I</td>
<td>15</td>
<td>10–22</td>
<td>150</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>$^{131}$I + steroids</td>
<td>0</td>
<td>0–2</td>
<td>145</td>
<td>–</td>
</tr>
<tr>
<td>Follow-up: 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

**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 \textsuperscript{131}I 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 \textsuperscript{131}I 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 \textsuperscript{131}I 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 \textsuperscript{131}I therapy.

The precise mechanism by which \textsuperscript{131}I 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 \textsuperscript{131}I 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

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