

# Graves' Ophthalmopathy: The Role of Thyroid Cross Reacting Autoantigens and The Effect of Thyroid Ablation

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**T**he pathogenesis and the treatment of Graves' Ophthalmopathy (GO), the most common extrathyroidal manifestation of Graves' disease, are still debated [reviewed in<sup>1</sup>]. Although associated with Graves' hyperthyroidism in most patients, GO may also occur with euthyroidism or hypothyroidism from Hashimoto's thyroiditis ("euthyroid Graves' disease"). GO precedes, occurs simultaneously with or follows hyperthyroidism in 13%, 43% and 44% of patients, respectively.<sup>2</sup> The time interval between the beginning of GO and the onset of hyperthyroidism is <18 months in 85% of patients.<sup>2</sup>

The natural history of GO is still poorly understood. Several factors contribute to this lack of clarity. In its classical study of 1945, Rundle described in GO an active phase, a stationary phase and a remission phase.<sup>3</sup> However, the severity of GO varies widely, with most patients presenting with a mild and non progressive ocular involvement, not requiring any active treatment and few being affected by a severe and disfiguring type, re-

quiring a prompt, active treatment.<sup>1</sup> Clinical evaluation of GO has widely changed in recent years. Whereas the older reports focused mainly on proptosis, it is now unanimously recognized that in the natural history of GO a hypothetical relationship between disease activity and severity exists.<sup>4</sup> Spontaneous retrobulbar pain, pain on eye movement, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, eyelid edema or fullness are evaluated to assess the activity of the GO, whereas diplopia and optic neuropathy are indexes of the severity of GO.<sup>5,6</sup> Differentiating the activity from the severity is crucial for a better evaluation and treatment of GO.<sup>1</sup> A protocol for the assessment of GO is available at the website of the European Group on Graves' Orbitopathy (EUGOGO) ([www/Eugogo.org](http://www/Eugogo.org)). Obviously, the clinical assessment of GO remains to some extent arbitrary and is influenced by the physician's own judgment and experience. To overcome this limitation, the A-mode ultrasound and the CT scan are widely used for a more objective evaluation of GO.

On these grounds it is not very surprising that only a few large reports on the "natural" history of GO have been published to date, [reviewed in<sup>1</sup>].<sup>7</sup> Moreover, different treat-

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ments for hyperthyroidism employed in these studies influenced the progression of GO and therefore made the history of their GO less “natural”, as it is widely accepted that any type of treatment can modify the evolution of GO. On the other hand, the choice of simply observing hyperthyroidism and GO, without any active treatment, would be unethical, particularly in the most severe forms of these two conditions.

Based on its histopathological characteristics, it is universally accepted that GO represents an autoimmune disorder. A leading pathogenetic hypothesis on GO development involves the role of autoreactive T lymphocytes, recognizing one or more autoantigens shared by the thyroid and the orbital tissue [reviewed in<sup>1,8</sup>]. In recent years many groups have attempted to identify the autoantigen(s) shared by the thyroid and the orbital tissue.

Because of its key role in the pathogenesis of Graves' hyperthyroidism, TSH receptor (TSHR) has been the main candidate. After its cloning in 1989, many authors have investigated the presence of the TSHR transcript and TSHR protein in the orbital tissue of GO patients [reviewed in<sup>1,8</sup>]. Many reports demonstrating the presence of TSHR mRNA in orbital tissue from patients with GO, as assessed by several techniques (reverse transcriptase PCR, northern blot, in situ hybridization, ribonuclease protection assay and real time PCR), have been published. Moreover, the presence of TSHR like immunoreactivity in GO orbital tissue has been confirmed in most studies by immunostaining with antibodies to the TSHR. Although intriguing, these results can not be considered definitive, because TSHR mRNA has been detected in other tissues, not involved in Graves' disease [reviewed in<sup>1,8</sup>].

Moreover, in the last 15 years, many authors have attempted to generate experimental models of Graves' disease using different approaches, based on TSHR immunization. After the first successful report,<sup>9</sup> in recent years other groups have described animal models of this disease [reviewed in<sup>8,10</sup>].

These studies have provided relevant data about the role of TSHR and TSHR autoantibodies in the pathogenesis of Graves' disease.<sup>11</sup> However, only few authors have reported ocular changes, of mild degree, in these animal models of Graves' disease.<sup>12,13</sup> Although of great interest, these results can not be considered definitive.<sup>8,14</sup>

In the 1970s Kriss<sup>15</sup> proposed thyroglobulin (Tg) as the link between thyroid autoimmunity and GO. We have recently published data supporting this hypothesis (16). Other autoantigens have been proposed to play a role in the pathogenesis of GO, and the question is still open [reviewed in<sup>1,8</sup>].

Therefore, experimental data available to date have not been able to identify the putative autoantigen(s) shared by the thyroid and the orbital tissue and its (their) putative role in the pathogenesis of GO.

Clinicians have extensively investigated the correlation between thyroid dysfunction and thyroid autoimmunity and the evolution of GO. It is generally accepted that a careful control of hyperthyroidism and of hypothyroidism has a beneficial effect on the course of GO.<sup>17</sup> As reported above, in many instances the onset of eye disease occurs simultaneously with or follows the institution of treatment for hyperthyroidism. The beneficial effect of the control of hyperthyroidism on GO may be due to the normalization of thyroid status per se or may be an effect of the modification of the underlying autoimmune process. Moreover, the effects of the different forms of treatment (antithyroid drugs, radioiodine therapy and thyroidectomy) for Graves' hyperthyroidism on the evolution of GO is debated. Antithyroid drug treatment does not appear to affect the course of GO.<sup>18</sup> Some authors, in the presence of severe GO, advise treatment of hyperthyroidism with anti-thyroid drugs.<sup>19</sup> Our approach is different, because of the large number of recurrences after drug withdrawal,<sup>20</sup> with the related reactivation of thyroid autoimmunity, that affects negatively the course of GO.<sup>21</sup> Therefore, in patients with GO, we suggest

achievement of permanent control of Graves' hyperthyroidism by ablation of thyroid tissue with radioiodine or thyroidectomy,<sup>22</sup> choosing the treatment for hyperthyroidism irrespective of GO presence or absence.<sup>1,23</sup> Radioiodine, a well-established treatment for Graves' hyperthyroidism, may worsen a pre-existing GO,<sup>18,24</sup> thus supporting a role for autoimmunity activation in GO. However, this aggravation can be prevented by a concomitant glucocorticoid administration.<sup>18,25</sup>

Although both drug and radioiodine treatments influence the immune response to the thyroid tissue and the evolution of GO, obviously neither of them can reduce significantly the amount of thyroid tissue and therefore the intrathyroidal cross reacting autoantigen(s) and autoreactive T-lymphocytes. Therefore, in order to corroborate the hypothesis that one or more autoantigens(s) shared by the thyroid and the orbit play a role in the orbital autoimmune reaction of GO and that the ablation of thyroid tissue might be beneficial for GO, we should look at the effect of more radical, i.e. surgical, treatment for Graves' hyperthyroidism on the course of GO.<sup>6</sup>

Both subtotal and near total thyroidectomy have been used for the treatment of Graves' disease, with discordant effects on the evolution of GO [reviewed in<sup>1</sup>]. In the 1960s Catz advocated the use of total thyroidectomy and I-131 to attain total thyroid ablation in order to improve GO as compared with subtotal thyroidectomy, that worsened GO.<sup>26</sup> The positive results of thyroid ablation obtained with total thyroidectomy or I-131 treatment were criticized by Werner, who reported the ineffectiveness of this approach.<sup>27</sup> The different results may be explained, at least partially, by a different degree of severity of GO, mild in the former series, severe in the latter.<sup>28</sup> In our experience neither subtotal nor total thyroidectomy have relevant effect on the progression of GO.<sup>29,30</sup>

In our opinion, two points are crucial to clarify the effect of thyroid ablation on the course of GO.

First, the concept of "thyroid ablation" is somewhat ambiguous. To evaluate the evolu-

tion of thyroid autoimmunity in relation to thyroid ablation we investigated 182 patients with differentiated thyroid carcinoma and positive circulating thyroid autoantibodies who underwent total thyroidectomy followed by ablation of residual thyroid tissue with I-131, as standard treatment for their differentiated thyroid carcinoma.<sup>31</sup> We definitely demonstrated that thyroid autoantibodies persist when even a small remnant of thyroid tissue is present and that total thyroid ablation, as demonstrated by negative whole body scan and undetectable circulating Tg (in patients with negative circulating autoantibodies to Tg), is required for the complete disappearance of thyroid autoantibodies. Turning back to the pathogenesis of GO, in our view these results support other authors' suggestions<sup>28,32</sup> that total thyroid ablation is required to correlate the effects of the disappearance of thyroid autoimmunity with the evolution of GO. In this regard, DeGroot showed an amelioration of GO after thyroid ablation in an uncontrolled study.<sup>33</sup>

The second consideration is that in patients with long-standing GO, the orbital autoimmune process is a well-established phenomenon that probably proceeds independently of the evolution of thyroid autoimmunity.<sup>34</sup> In these patients thyroidectomy would be unable to improve GO. This is in agreement with the above mentioned dispute about the effect of total thyroidectomy on the evolution of GO.<sup>27,28</sup>

In summary, prospective, randomized and controlled clinical studies are required to confirm that total thyroid ablation, as obtained by total thyroidectomy plus I-131 treatment, improve the course of GO, thus supporting the hypothesis of the existence of a shared antigen(s) between the thyroid and the orbital tissue. An accurate selection of patients, including those with initial GO only, is mandatory. We are currently investigating this issue. Preliminary data show that, in patients with mild to moderate GO, all treated with glucocorticoid, total thyroid ablation is more effective than total thyroidectomy or methimazole in improving the course of GO.

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