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REVIEW

# Total thyroid ablation in Graves' orbitopathy

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**Abstract** Graves' orbitopathy (GO) is an autoimmune condition almost always associated with autoimmune thyroid disease, especially Graves' disease (GD). According to the most widely accepted model, the autoantigens responsible for GO would include molecules expressed by thyroid epithelial cells that are present also in orbital tissues. The high likelihood that the etiologies of GO and of the underlying autoimmune thyroid diseases are somehow linked is confirmed by the very close relationship between GO, the onset and the course of Graves' diseases, the size of the thyroid gland, and most importantly, thyroid function and thyroid treatment. Based on these considerations, it has been proposed that complete removal of thyroid antigens and of thyroid infiltrating lymphocytes, the so-called total thyroid ablation (TTA), may be followed by an attenuation of the immune reaction against orbital antigens, and ultimately by an amelioration of GO. The possibility that TTA, achieved by near total thyroidectomy followed by radioiodine, may be beneficial for GO was initially suggested by two retrospective studies and more recently by two prospective, randomized clinical trials conducted in patients with moderate GO treated with intravenous glucocorticoids. Although there seemed to be no difference in the long term, compared with near total thyroidectomy alone TTA was associated with a shorter time required for GO to improve, or anyway to reach its best possible outcome, and with a lesser requirement for additional treatments for GO to improve. Whether this is sufficient to offer ablation to patients remains a matter of discussion. At present, this procedure could be offered only to patients scheduled to thyroidectomy and glucocorticoid treatment.

**Keywords** Graves' disease · Graves' orbitopathy · Thyroidectomy · Radioiodine · Total thyroid ablation

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## Introduction

Graves' orbitopathy (GO) is a disfiguring and rather disabling disease that impairs profoundly the quality of life of affected patients [1, 2]. GO is almost invariably associated with autoimmune thyroid disease (AITD), namely Graves' disease (GD) in the vast majority of cases (~95 %), and less frequently autoimmune thyroiditis (AT) or subclinical thyroid autoimmunity (the so-called euthyroid GO) [1–5]. The association between GO and AITD, as well as the influence of the underlying thyroid disease and of its treatment on the natural history of GO [1, 2, 4, 5], have quite obviously suggested the existence of a close relationship between the thyroid gland and the affected orbital tissues [7, 8]. In particular, it has been proposed that GO would be the consequence of autoimmunity against antigens that are present both in the thyroid and in orbital tissues [7, 8], based on which it has been proposed that complete elimination of thyroid antigens (total thyroid ablation, TTA), may be beneficial for GO [9]. In this regard, a number of studies, either retrospective or, more recently, prospective and randomized [10–15], support a possible role of TTA in GO. Here we review the data available on this procedure, preceded by a brief review of the relationship between GO and the thyroid gland, both concerning the pathogenesis of GO and the

clinical impact of the underlying thyroid disease and of its treatment on the natural history of GO.

## Thyroid autoantigens possibly involved in the pathogenesis of GO

In spite the efforts of many investigators over nearly one century, the pathogenesis of GO has not been clarified with certainty [7, 8]. Based on its association with AITD [4, 5], on the presence of a lymphocytic infiltrate of orbital tissues and on the fairly good response to glucocorticoid-induced immunosuppression [16–18], it is almost universally accepted that GO is an autoimmune condition. According to the most widely accepted model, the autoantigens responsible for GO would include molecules expressed by thyroid epithelial cells that are present also in orbital tissues. The presence of these shared antigens in orbital tissues would reflect either their constitutive expression, or the binding of molecules released from the thyroid together with autoreactive T lymphocytes [7, 8].

The TSH receptor (TSH-R), the autoantigen responsible for the thyroid manifestations of GD [19], is commonly regarded as the most suitable candidate autoantigen also for GO. TSH-R is expressed and functionally active in orbital tissues [7, 8]. Thus, either TSH itself, patient TSH-R stimulating immunoglobulins, or more recently, a monoclonal anti-TSH-R stimulating antibody, is able to stimulate synthesis of hyaluronic acid as well as adipogenesis in orbital fibroblasts from GO patients [20–22]. In addition, GO is almost invariably associated with the presence of circulating autoantibodies against the TSH-R [1, 2, 23], regardless of the underlying thyroid disease [5], and there seems to be a close relationship between the severity and the activity of GO and the presence and levels of anti-TSH-R autoantibodies [24], although this finding was not always confirmed [6, 25]. Animal models of GO also seem to support a role of TSH-R in its pathogenesis. Genetic immunization of mice with TSH-R is followed by a syndrome that to some extent resembles GD [26]. Although in the majority of animal models of GD no eye changes were observed, features of GO were reported by two studies. In the first one, eye alterations resembling GO were observed [27], but the results were not reproduced by the same authors in a subsequent investigation, presumably because of environmental influences [28]. More recently, another model of GO was developed by genetic immunization of BALB/c mice with the human TSH-R A-subunit [29]. Although mice were hypo- rather than hyperthyroid, features of GO were observed at histology and by magnetic resonance imaging. Recent studies have provided evidence that, by acting in concert with TSH-R, the insulin-like growth factor one receptor (IGF-1-R), which is expressed by orbital fibroblasts and orbital fibrocytes, seems to be necessary for TSH-R-driven autoimmunity [30].

Another hypothesis involving thyroglobulin (Tg) was originally formulated by Kriss [31], who, in the early 70s, first postulated that the initiating event in the pathogenesis of GO may be the deposition and accumulation of one or more soluble thyroid antigens, following their massive release from the thyroid, as it occurs during thyrotoxicosis or after radioiodine treatment. Once in the orbit thyroid autoantigens would trigger an autoimmune reaction against orbital tissues. Because of its abundance within the thyroid and of its solubility, the most suitable candidate was considered to be thyroglobulin (Tg) and, as a matter of fact, Tg of thyroid origin (containing thyroid hormone residues) was found in orbital tissues of GD patients in strict relation with radioiodine treatment [32–34]. In addition, Tg binding sites were demonstrated in cultured orbital fibroblasts [35], although no Tg-anti-Tg immune complexes were found in orbital tissues and no signs of GO have been reported in experimental models of AT induced in mice by immunization with Tg [34]. Thus, whether Tg is involved in the pathogenesis of GO remains to be established.

## Relationship between hyperthyroidism, thyroid treatment and GO

The high likelihood that the etiologies of GO and AITD are somehow linked is confirmed by the very close relationship between GO, the onset and the course of the underlying thyroid disease, the size of the thyroid gland, and most importantly, thyroid function and thyroid treatment.

As mentioned above, GO is observed mostly in GD patients and there is a close temporal relationship between the onset of Graves' hyperthyroidism and that of GO [36–38]. On the same line, the severity of GO seems to parallel that of GD, as somehow indicated by a recent study in which the size of the thyroid gland (thyroid volume) was found to correlate with the degree of GO [25].

In further support of a close relationship between the pathogenetic mechanism of GD and GO, the degree of hyperthyroidism seems to correlate with the presence and the severity of GO. The data available on this issue can be summarized as follows: (1) GO is more severe in patients with untreated hyperthyroidism [39]; (2) the possibility of worsening of GO in patients with GD undergoing radioiodine therapy is greater in those who have received more than one dose of radioiodine [40, 41]; and (3) after treatment of hyperthyroidism with a course of anti-thyroid drugs, the possibility of deterioration in the GO is greater in patients who undergo relapse of hyperthyroidism [42]. In theory, these findings could be also interpreted as due to a direct relationship between GO and hyperthyroidism that

goes beyond a pathogenetic association of GO with thyroid autoimmunity. Thus, it is possible that, while not being the cause or at least not the only one, hyperthyroidism per se may influence the onset and the subsequent progression of GO. In this regard, the excess of thyroid hormones determines tissue oxidative stress, which is one of the factors contributing the inflammatory changes of the orbit in GO [1]. However, as mentioned above, it is also possible, and perhaps more likely, that the contribution of hyperthyroidism is minimal and that the association between hyperthyroidism and GO and the greater severity of GO in patients with untreated hyperthyroidism reflect the fact that GO and hyperthyroidism are due to the same alteration of the immune system against the thyroid and orbital antigens [7, 8]. Each activation or re-activation of the immune system against these antigens may correspond to a temporal association between activation or re-activation of both hyperthyroidism and GO. According to this interpretation, half of the patients with GD in which GO appears after hyperthyroidism, are euthyroid on anti-thyroid drugs, indicating that hyperthyroidism is not a necessary condition for the development of GO. Moreover, albeit rarely, GO can occur in patients with autoimmune thyroiditis or in absence of clinically relevant thyroid diseases, thereby confirming that hyperthyroidism is not necessary for GO to develop [4, 5].

In support of a relationship between hyperthyroidism and GO, after the beginning of anti-thyroid drugs there can be a slight improvement of GO [43, 44]. Based on animal studies, an immune suppressive action is anecdotally attributed to methimazole, although the majority of experts in the field believe that this is at least questionable [45]. Thus, although the improvement of GO on methimazole may in theory reflect a direct action of the drug on the immune system, this is more likely to be the consequence of a spontaneous improvement of GO, which is known from the natural history of the disease [4, 6] or, alternatively, the correction of hyperthyroidism. On the other hand, in a study conducted in a large number of patients, Bartalena et al. [46] observed that treatment with methimazole does not affect the course of GO. Similar conclusions were reached by other previous studies [47, 48] and, in addition, in some patients GO can appear in spite of the correction of hyperthyroidism with methimazole [49].

The existence of a relationship between radioiodine treatment and the onset or worsening of GO has been a matter of controversy since a long time [50]. However, data from randomized clinical trials seem to indicate a negative action of radioiodine on GO, both in terms of de-novo appearance and of worsening of a pre-existing eye disease, presumably due to the massive release of thyroid antigens that follows radioiodine therapy, with consequent activation or re-activation of the immune system against the same (or similar) antigens expressed by orbital tissues. In support of this hypothesis, treatment with radioiodine is followed by an increase in the levels of autoantibodies against the TSH-R, which is not observed after thyroidectomy or during treatment with anti-thyroid drugs [51]. In two different studies, Bartalena et al. [46, 52] observed a worsening or a de-novo appearance of GO after radioiodine, which in the larger study (450 patients) was estimated to be ~15 and ~2 %, respectively. A progression of GO after radioiodine was observed also by Tallstedt et al. [53]. However, in a subsequent study the same authors did not confirm the conclusion that radioiodine was responsible for GO progression [54]. Thus, in the latter study [54], unlike in the first study [53], patients were given with L-thyroxine early after radioiodine, which was associated with a reduced rate of GO progression compared to patients treated with L-thyroxine only after the onset of hypothyroidism. Thus, they concluded that worsening of GO after radioiodine was due to hypothyroidism [54]. On the other hand, it must be underlined that also in the larger study of Bartalena et al. [46] L-thyroxine was started early. It is possible that the differences between these studies depend on the different number of patients, but also on differences in inclusion criteria, levels of activity and severity of GO, and duration of the eye disease. Considering that the study from Bartalena et al. [46] was by far the largest, it is presumable that it can offer an information closer to the reality, and that, therefore, in some patients radioiodine therapy may favor a progression of GO regardless of the earliness of L-thyroxine replacement for hypothyroidism, a condition which, in any case, can by itself contribute the progression of GO.

In spite of some retrospective studies that showed an improvement of GO in a proportion of patients ranging between ~50 and ~80 % following thyroidectomy [55–57], the majority of studies seems to exclude an effect of either total or subtotal thyroidectomy on GO [58–60]. It must be underlined that complete removal of the thyroid gland is never performed, because removal of the thyroid tissue adherent to the adjacent anatomical structures increases the risk of surgical complications, which can probably explain why GO is not affected by thyroidectomy. Thus, if complete removal of thyroid tissue could be performed with consequent elimination of the thyroid antigens, according to the "shared antigens" pathogenetic hypothesis, one would expect an attenuation of the autoimmune reaction against the same antigens expressed in the orbit and ultimately an amelioration of GO. Because of this reason, TTA, obtained by near total thyroidectomy followed by radioiodine, has been proposed in patients with GO.

## TTA

In patients with differentiated thyroid cancer and circulating autoantibodies against thyroglobulin and/or thyroid

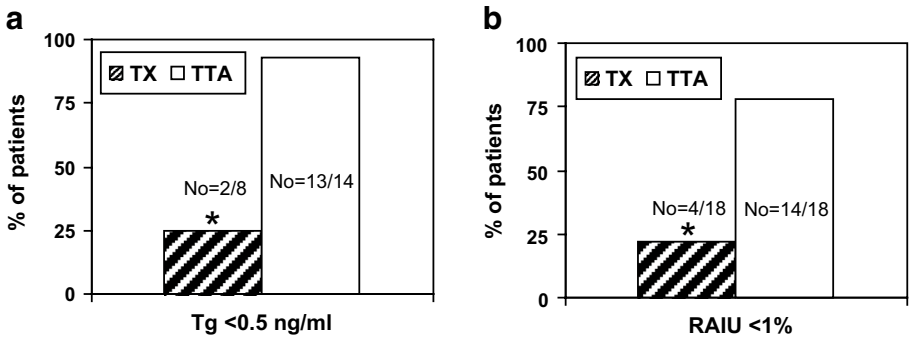


**Fig. 1** Assessment of ablation in a random sample of patients with Graves' orbitopathy after $LT_4$ withdrawal, treated with near total thyroidectomy (TX) or with total thyroid ablation (TTA), namely near total thyroidectomy followed by radioiodine. **a** Prevalence of patients with serum Tg > 0.5 ng/ml in the absence of anti-Tg autoantibodies; $*P = 0.0049$ by Fisher exact test; **b** prevalence of patients with a 3 h radioiodine uptake >1 %; $*P = 0.002$ by Fisher exact test. Modified from Ref. 13 (©Endocrine Society, with permission)

peroxidase, complete elimination of thyroid tissue obtained by near total thyroidectomy and radioiodine, is followed by disappearance of circulating anti-thyroid antibodies within 3–5 years [61]. This observation suggests that the elimination of thyroid antigens induces an attenuation of the immune response against them. If, as postulated, GO is due to an autoimmune response against antigens expressed by the thyroid and by orbital tissues, it would be reasonable to hypothesize that removal of thyroid antigens and of thyroid infiltrating lymphocytes may be followed by an attenuation of the immune reaction against orbital antigens, and ultimately by an amelioration of GO.

The possibility that TTA may be beneficial for GO was first proposed by Catz and Perzik in the 1960s [10]. In 1996, De Groot and Benjasuratwong, in a retrospective study conducted in a small group of patients, showed an improvement of GO following TTA [11]. Likewise, in a subsequent retrospective study conducted in Italy, Moleti et al. [12] came to the same conclusions.

The first prospective, randomized study on this topic was conducted in 60 patients with mild-to-moderate GO treated with intravenous glucocorticoids, 30 of whom after near total thyroidectomy, and 30 after TTA (near total thyroidectomy followed by 30 mCi of radioiodine) [13]. To assess the extent of ablation, at the end of the study a sample of patients withdrew $LT_4$ and underwent a serum Tg measurement (only if TgAb negative) and a radioiodine uptake (RAIU) test. As shown in Fig. 1a, only 25 % of patients in the thyroidectomy group had Tg values <0.5 µg/l, whereas this was the case in ~95 % of patients who underwent TTA, suggesting that nearly all patients in the latter group were actually ablated. Likewise, only ~20 % of patients in the thyroidectomy group had a 3 h RAIU value <1.0 % compared with ~80 % in the TTA group (Fig. 1b), again indicating that the majority of patients subjected to near total thyroidectomy followed by radioiodine were in fact ablated

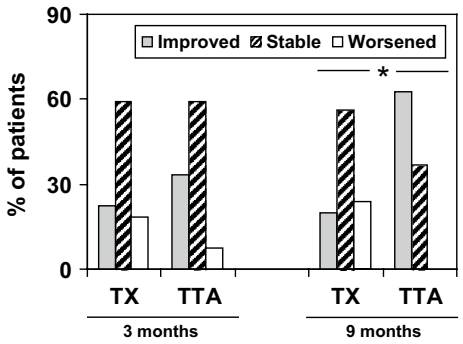


**Fig. 2** Overall outcome of Graves' orbitopathy after near total thyroidectomy (TX) or total thyroid ablation (TTA) in patients treated with intravenous glucocorticoids. $*P = 0.0014$ by Fisher exact test. Modified from Ref. 13 (©Endocrine Society, with permission)

[13]. As shown in Fig. 2, the distribution of GO outcome at 9 months was significantly more favorable in the TTA group, and although no significant difference was observed at 3 months, the cumulative difference between the two groups at 3 and 9 months was significant, suggesting a better outcome of GO after glucocorticoid treatment in patients who had undergone TTA [13].

In a continuation of the same study [14], most of the patients (52/60) were re-evaluated after a long period of time, up to ~130 months after the end of glucocorticoid treatment. The overall GO outcome at the end of follow-up (~90 months) was similar in the two groups, indicating that in the long term the beneficial effects of ablation are lost. However, as shown in Fig. 3, an analysis of the intermediate visits showed that the time required to reach the best possible GO outcome was longer in thyroidectomy than in the TTA group, as was the time for GO to improve [14]. Depending on the features of GO, over the years additional treatments had been offered, including

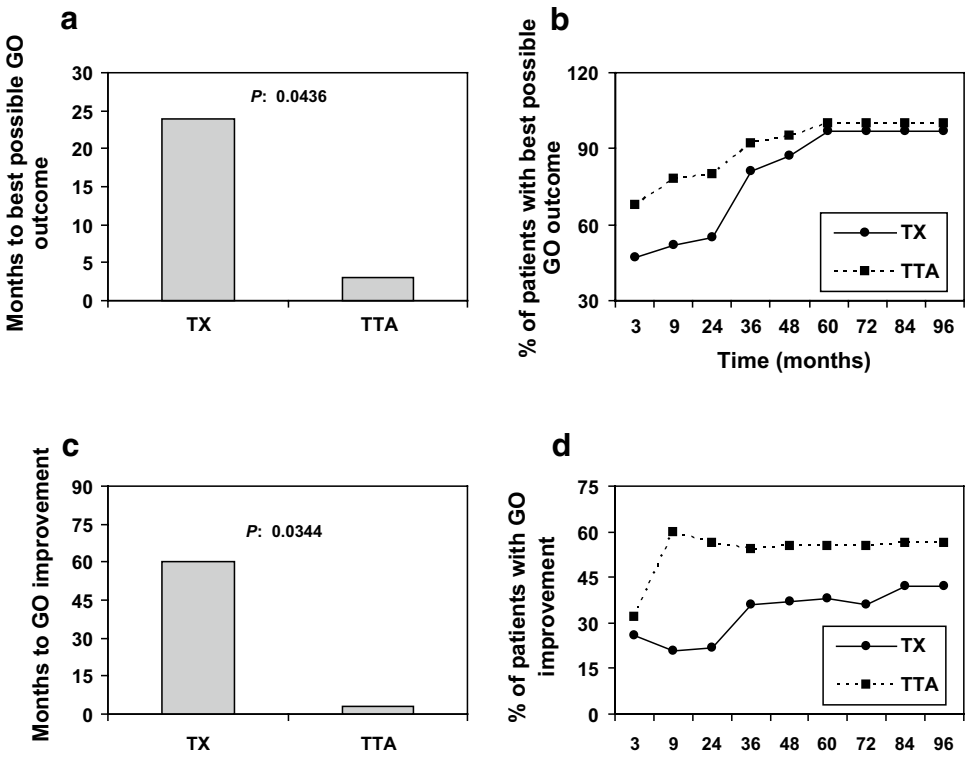


**Fig. 3** **a** Median time required to achieve the best possible outcome (the outcome observed at the end of the follow-up) of Graves' Orbitopathy in patients treated with near total thyroidectomy (TX) or total thyroid ablation (TTA), followed by intravenous glucocorticoids; **b** percent of patients reaching the best possible GO outcome over time; **c** median time required to reach an improvement of GO; **d** percent of patients with GO improvement over time. **P* values were obtained by Fisher exact test. Modified from Ref. 14 (©Endocrine Society, with permission)

additional GC, orbital radiotherapy, orbital decompression, muscle and/or eyelid surgery, which determined an amelioration of GO compared with the outcome at 9 months in ~30 % of patients treated with near total thyroidectomy, but only in ~4 % of patients treated with TTA, suggesting that additional treatments were necessary for GO to improve in the thyroidectomy group, but not in the ablation group [14]. Based on these findings, it can be concluded that, compared with thyroidectomy alone, TTA allows the achievement of the best possible outcome and of an improvement of GO within a shorter period of time.

In another randomized trial, Moleti et al. [15] also found a better short-term outcome of GO in patients treated with intravenous glucocorticoids who underwent TTA compared with those treated with near total thyroidectomy only. The only difference with our study was that they performed radioiodine treatment after the administration of recombinant human TSH, whereas in our study ablation was performed after withdrawal of $LT_4$ [13]. In this regard, the risks of worsening of GO due to $LT_4$ withdrawal are quite well known, as also reported recently [62].

## Conclusive remarks

Treatment of hyperthyroidism in patients with GO is controversial. Whereas a conservative strategy based on anti-thyroid drugs is favored by some; others, including ourselves, advocate an ablative strategy. The latter is based on a proposed pathogenetic hypothesis according to which GO would reflect autoimmunity against antigens present both in thyroid and in orbital tissues, the removal of which would be beneficial for GO. After thyroidectomy alone or radioiodine alone, ablation is rarely complete and therefore, TTA, performed by near total thyroidectomy followed by radioiodine, has been proposed. Two randomized trials have shown a beneficial effect of TTA in the short term compared with thyroidectomy alone in patients with moderate GO given intravenous glucocorticoids. Although there seems to be no difference in the long term, TTA is associated with a shorter time required for GO to improve, or anyway to reach its possible best outcome, and, in addition, with a lesser requirement for additional treatments for GO to improve.

There are several questions that remain to be answered concerning ablation in general and TTA in particular. First, it has not been established whether an ablative strategy (either with thyroidectomy, radioiodine or both) is preferable to a conservative one (with anti-thyroid drugs). Second, patients in the two randomized studies on TTA were given glucocorticoids, and it is therefore not known whether TTA is beneficial also in patients not given this treatment. Third, patients in the two randomized studies had moderate GO and therefore, it is not known whether TTA is effective for milder forms of GO.

In conclusion, TTA may be a possible strategy for GO. The apparent advantages are a better GO outcome in the short term, a shorter period required for GO to improve, and the need for lesser additional treatments for GO to improve. Whether this is sufficient to offer ablation to patients remains a matter of discussion. At present, this procedure could be offered only to patients scheduled to thyroidectomy and glucocorticoid treatment.

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**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed Consent** No Informed Consent.

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