The Effect of Early Thyroidectomy on the Course of Active Graves' Orbitopathy (GO): A Retrospective Case Study

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Key words
- thyroid treatment
- thyroidectomy
- ATD
- course of GO

Abstract

The aim of the work was to investigate the effect of early thyroidectomy on the course of active Graves' orbitopathy (GO) in patients with low probability of remission [high TSH receptor antibody (TRAb) serum levels, severe GO] compared to that of continued therapy with antithyroid drugs. Two cohorts were evaluated retrospectively (total n = 92 patients with active GO, CAS ≥ 4). Forty-six patients underwent early thyroidectomy (Tx-group) 6 ± 2 months after initiation of antithyroid drug (ATD) therapy, while ATD was continued for another 6 ± 2 months in the ATD-group (n = 46). These controls were consecutively chosen from a database and matched to the Tx-group. GO was evaluated (activity, severity, TRAb) at baseline and at 6 month follow-up. At baseline, both cohorts were virtually identical as to disease severity, activity and duration, as well as prior anti-inflammatory treatment, age, gender, and smoking behavior. At 6 month follow-up, NOSPECS severity score was significantly decreased within each group, but did not differ between both groups. However, significantly more patients of the Tx-group presented with inactive GO (89.1 vs. 67.4 %, $^{*}p = 0.02$), and mean CAS score was significantly lower in Tx-group (2.1) than in ADT-group (2.8; $^{*}p = 0.02$) at the end of follow-up. TRAb levels declined in both groups (Tx-group: from 18.6 to 5.2 vs. ATD-group: 12.8–3.2 IU/l, $p_0 = 0.07$, $p_{6\text{months}} = 0.32$). Residual GO activity was lower in Tx-group, associated with a higher rate of inactivation of GO. This allows an earlier initiation of ophthalmosurgical rehabilitation in patients with severe GO, which may positively influence quality of life of the patients.

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Introduction

Graves' orbitopathy (GO) is an inflammatory orbital disease that is mostly associated with autoimmune Graves' disease. During the course of GO, patients may develop lid retraction, marked periorbital swelling, impaired ocular motility due to fibrotic changes of the extraocular muscles, disfiguring proptosis, and optic nerve compression. Patients with severe disease suffer from major functional deficits and facial disfigurement. About half of the patients with Graves' hyperthyroidism develop GO, which is closely related to onset and course of the thyroiditis: it usually occurs simultaneously, occasionally after onset of thyroid disease due to an unfavorable course, and only rarely before clinically evident hyperthyroidism. Autoantigens responsible for GO include molecules expressed by thyroid epithelial cells as well as by orbital tissues. Especially, interaction between the TSH-receptor (TSHR) and TSH-receptor autoantibodies (TRAb) is pivotal to the pathogenesis of hyperthyroidism and orbital disease [1,2]. Anti-inflammatory therapy may inactivate orbital inflammation in 70–80 % of cases; however, complete remission of orbital changes is rare [3]. Commonly, surgical intervention (orbital surgery, squint- and lid corrections) is necessary to restore function and appearance in moderate to severe disease stages. As prerequisites for ophthalmosurgery are stable euthyroidism and inactive GO for at least 6 months [4], it takes 1.5–2 years until surgical rehabilitation is initiated.

In Europe, treatment of hyperthyroidism usually includes thyreostatic pharmacotherapy for 12–18 months [5]. After termination of thyreostatics, the overall relapse rate of hyperthyroidism is roughly 50 %. Large thyroid volume, nicotine consumption, advanced age and, notably, high serum TRAb activities increase the risk of relapse [6]. Studies using a second generation

human TRAb assay show that relapse or remission of hyperthyroidism correlate with TRAb serum levels and the severity of eye disease 6, 12, or 18 months after initiation of thyreostatic therapy (reviewed in [7]). As early as 6 months after the beginning of antithyroid drug treatment in patients with TRAb serum levels ≥10 IU/l remission rates of hyperthyroidism are rather low with 3% [8]. Comparably low remission rates of about 8% occur in patients with severe GO [9]. These low remission rates raise the question of the optimal time point of definite thyroid treatment for these patients. In those cases either thyroidectomy and/or radioiodine therapy, is indicated, particularly as removal of thyroid antigens by attenuating autoimmunity, may be beneficial for GO [10].

Antithyroid drug (ATD) therapy is most favorable in the early phase of the disease, and, if chosen as initial therapy, it is accompanied by a 10% risk of further deterioration of GO in comparison to 16% after thyroidectomy, and 33% after radioiodine therapy as published by Tallstedt et al. [11]. However, in this randomized clinical trial only patients without and with mild GO stages were included. Other observational studies with widely variable inclusion criteria led to the assumption that patients with active orbital inflammation may benefit from early thyroidectomy [12, 13]. Several studies concerning the influence of thyroidectomy with or without accompanying radioiodine therapy (total ablation) are available in the later phase of GO after a longer course of antithyroid drug therapy (Marcocci 11±4 months or De Bellis 21.23±11.2). Marcocci and colleagues reported that the course of Graves' orbitopathy is not influenced by near total thyroidectomy in comparison to methimazole therapy [14]. De Bellis et al. reported a much later and less marked improvement of GO with persistence of TRAb in the methimazole therapy group in comparison to thyroidectomy with and without postoperative radioiodine therapy [15]. However, more recent studies substantiate the hypothesis that patients with moderate to severe active GO might benefit from an early thyroidectomy in the sense of faster and more profound improvement of GO [16–19].

We now report findings from a retrospective case control study on the effect of early thyroidectomy on moderate to severe, active GO when compared to standard antithyroid drug treatment.

Patients and Methods

We performed a retrospective cohort study, including a total of 92 GO patients of Caucasian origin. All patients had a CAS > 4 at baseline, having active GO. Patients were included into early thyroidectomy group (Tx-group), if they underwent total thyroidectomy 6±2 months after initiation of thyreostatic therapy, and GO was moderate to severe, and if they had developed orbitopathy within 6 months before or after the onset of hyperthyroidism, at least short before baseline examination, and if follow-up after thyroidectomy was 6±2 months (n = 46). These patients were compared to a control group (n = 46), which were followed after 6 months of ATD for another 6±2 with further antithyroid treatment (ATD-group). Controls were consecutively picked from a patient database that had been initiated in 11/2000, containing data on more than 1000 patients suffering from Graves' orbitopathy at the time of this study. Control patients were eligible, if they were first examined 6±2 months after initiation of antithyroid drug therapy, if antithyroid drugs had been administered for at least 12±2 months (until the end of follow-up period), if they had developed orbitopathy within 6 months before or after the onset of hyperthyroidism at least short before baseline examination, and if they matched for a patient in the Tx-group regarding previous anti-inflammatory therapy and severity of GO. If there were more matched patients, patients with the closest referrals to the thyroidectomy patients were chosen for the more common situations.

The effect of both therapeutical approaches on the course of orbital inflammation was evaluated at baseline and after 6±2 months. Clinical activity score (CAS), NOSPECS severity score, serum TRAb activity, inactivation rate, and the necessity of anti-inflammatory therapy served as outcome parameters. Visual acuity, lid fissure width, downward motility of the upper lid, proptosis, signs of inflammation (rubor and swelling of lids and conjunctiva), and extraocular motility (monocular excursions measured with Kestenbaum glasses) were assessed in each patient. Consecutive examinations were performed by the same investigator. In case of reduced visual acuity, the cornea was stained with fluorescein, and if slit lamp and fundus examination revealed normal anatomical conditions, visual evoked potentials were carried out to examine optic nerve function. The clinical activity score (CAS) was assessed as described by Mourits [20]. Disease severity was estimated using a previously described modified NOSPECS score [21].

Anti-inflammatory treatment during follow-up

During follow-up, anti-inflammatory therapy was offered to all patients with active orbitopathy (CAS ≥ 4) who had no therapy yet, who had i. v. steroids but not the full cumulative dose of 4.5 g and who had motility impairment but no irradiation yet. Prednisone (Prednisolut) was given intravenously in a cumulative dose of 2.68 g for 6 weeks [once every week 500 mg (3×) or 250 mg (3×)], and on all other days 10 mg oral fluocortisone (Fluocortulone), which was tapered out over 10 days and this was repeated when activity persisted. In cases with impaired ocular motility, additional orbital irradiation (total absorbed doses between 12–20 Gray) was performed. However, despite CAS ≥ 4 10 patients of the Tx-group and 13 of the ATD-group did not receive any treatment during observation period. These patients had a good quality of life despite CAS ≥ 4 and did not wish any further treatment.

TRAb assay

TRAb serum levels were measured with a second generation TSH-binding inhibitory (TBII) assay based on the human recombinant TSH-receptor (TRAK human LIA®, B.R.A.H.M.S AG, Hennigsdorf/Berlin, Germany) [22]. This assay is calibrated in international units (IU), based on the WHO-reference standard MRC 90/672. 50% inhibition of tracer binding corresponds to 7–8 IU/l. Values ≥ 1.5 IU/l (approx. 10% tracer binding) were regarded as positive, values between 1 and 1.5 IU/l as borderline, and values < 1.0 IU/l as negative.

Thyroidectomy

Surgery was performed under general anesthesia. Total thyroidectomy was conducted through a central neck incision. Routinely, both recurrent laryngeal nerves were visualized and dissected free. The parathyroid glands were meticulously preserved and in case of insufficient perfusion autotransplanted prior the closure of the skin. A video-assisted approach was used in selected cases.

Table 1 Patient characteristics at baseline.

Patients characteristics at baseline	Early thyroidectomy group	p	ATD-Group
Number of patients	46		46
Age (years)[a]	48.8 (20–68)	0.6 ns	50.8 (27–78)
Gender Female/Male (%)	87/13	0.28 ns	76/24
Smoker/Non-smoker (%)	70/30	0.38 ns	59/41
Classification mild * /severe	9/37	0.57 ns	6/40
Duration of GD since initiation ATD (months) [a]	6 (4–8)	0.93 ns	6 (4–8)
Duration of GO since initiation ATD (months) [a]	0 (−6 to 6)	0.22 ns	0 (−6 to 6)
Duration of GD until Thyroidectomy (months) [a]	6 (4–8)		
Patients with active GO (CAS ≥ 4) (%) [b]	100	1.0 ns	100
Activity of GO (CAS score) [c]	5.9 ± 1.5	0.39 ns	5.7 ± 1.5
Severity of GO (NOSPECS score) [c]	7 ± 2.1	0.46 ns	7.35 ± 2.4
TRAb level [a]	18.6 (0.9–123.7)	0.07 ns	12.8 (0.4–97.5)
Anti-inflammatory therapy prior observation period (%) (No therapy/Steroids/Steroids and orbital irradiation)	39/41/20	1.0 ns	39/41/20
Protrusio: Hertel R/L pathological/normal (%) [d]	70/30	0.87 ns	67/33
Mean Edema Score (Injection/Chemosis/Swelling/Irritation)	7.4	0.2 ns	6.9
Mean Edema score pathological (≥ 2) (%)	100	1.0 ns	100

* Inclusive 1 mild-moderate in Thyroidectomy- and 3 in ATD-group

[a] Data expressed as median (range)

[b] Active GO: CAS ≥ 4, Inactive GO: CAS < 4

[c] Data expressed as mean ± SD

[d] Hertel pathological (≥ 17 mm)/normal (< 17 mm)

Statistical analysis

Group comparisons were tested for statistical difference with the non-parametric Mann-Whitney test (Graph pad prism 5.0) analyzing parameters that did not follow Gaussian distribution, such as TRAb activities, CAS, and NOSPECS. Fisher's exact T-Test, Wilcoxon rank and Chi-Square test were used for cross tables of patient-groups vs. binary variable as stated (e.g., gender, smoking status, inactivation, and prior anti-inflammatory therapy). All p-values equal to or lower than 5% (≤0.05) were regarded as significant.

Ethical approvement

This study was approved by the Medical Ethics Committee of the University of Duisburg-Essen, Germany. Written consent to be included in our database and to have blood exams performed was obtained from all participants.

Results

Both cohorts were very well matched. At baseline (**Table 1**) there were no statistically significant inter-group differences concerning age (median age: Tx-group 48.8 years, ATD-group 50.8 years, p = 0.6) or gender (Tx-group 87% female/13% male patients, ATD-group 76% female/24% male patients, p = 0.28). Seventy percent of patients of the Tx-group and 59% of the ATD-group were smokers (p = 0.38). In the Tx-group, mean CAS was 5.9 vs. 5.7 in the ATD-group (p = 0.39), and in both groups all patients had active GO (CAS ≥ 4). Severity of GO at baseline was comparable in both groups (mean NOSPECS score: Tx-group 7, ATD-group 7.35, p = 0.46). TRAb activities in serum were higher in the Tx-group (mean 23.8, median 18.6 IU/l) in comparison to ATD-group (mean 16.3, median 12.8 IU/l), the difference was not significant (p = 0.07). In both groups, 61% of patients had received steroids, and 20% of these patients had had orbital irradiation, 39% had not received any anti-inflammatory therapy prior to observation period (p = 1.0). Protrusio of the eye measured with a Hertel Exophthalmometer was pathological (≥ 17 mm) in 70% of patients in Tx-group and in 67% of patients in ATD-group (p = 0.87). All patients in both group presented with a pathological Edema score of 2 or higher, mean Edema score in Tx-group was 7.4 and in ATD-group 6.9 (p = 0.2) (**Table 1**, **Fig. 1**).

At follow-up 6 ± 2 months after baseline disease severity (mean NOSPECS Tx-group 5.7, ATD-group 5.9, p = 0.56) as well as serum TRAb activities (median TRAb level Tx-group 5.2, ATD-group 3.2, p = 0.36) had declined significantly in both cohorts, but with no significant inter-group differences between thyroidectomized and control patients (**Table 2**, **Fig. 1**). Protrusio of the eye was still pathological (≥ 17 mm) in 66.3% of patients in Early Tx-group and in 60.9% of patients in ATD-group (p = 0.54). All patients in both groups presented with a pathological Edema score of 2 or higher, mean Edema score in Tx-group was 5.1 and in ATD-group 4.6 (p = 0.38) (**Table 2**). Anti-inflammatory therapy during follow-up was not different in both groups. Additional doses of i.v. steroids pulses were administered in 12 patients of the Tx-group and 10 patients of the ATD-group. Twenty-four (Tx-group) as well as 23 (ATD-group) patients received steroids in combination with orbital irradiation due to persistent motility deficits (cumulative steroid doses remained < 4.5 g). Ten thyroidectomized patients vs. 13 in ATD-group had not received any anti-inflammatory therapy according to patients wishes despite CAS ≥ 4 due to good quality of life (p = 0.8) (**Table 2**, **Fig. 2**).

Clinical activity of GO declined in both groups, but more in the Tx-group (mean CAS at 12 months Tx-group 2.1, ATD-group 2.8, * p = 0.03) (**Table 2**, **Fig. 1**). The inactivation rate (Tx-group 89.1%, ATD-group 67.4%, * p = 0.02) was significantly higher in the early thyroidectomized cohort (**Table 2**, **Fig. 3**).

Discussion

The management of active Graves' orbitopathy (GO) can be a challenging therapeutic dilemma due to its pathogenic complexity, disease heterogeneity, clinical unpredictability, and ocular morbidity. The relation between orbital inflammation and treatment of hyperthyroidism has been subject of many studies

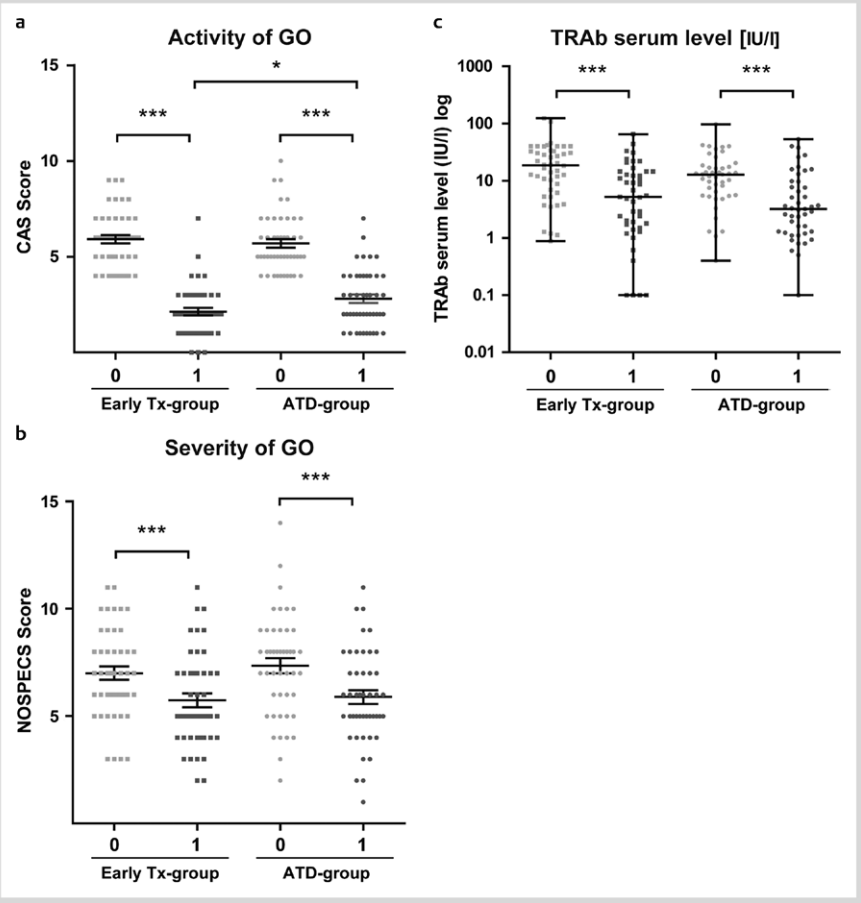

Fig. 1 **a**: Reduction of Clinical Activity of GO: Mean CAS score declined significantly from baseline (0) to 6 months follow-up (1) as well in Early Thyroidectomy group (Early Tx-group; from 5.9 to 2.1, *** $p<0.0001$) as in ATD-group (from 5.7 to 2.8, *** $p<0.0001$). However, patients of the Early Tx group presented with a significantly lower CAS of GO when compared to ATD-group at the end of follow-up (* $p=0.03$). **b**: Reduction of severity of GO. Mean NOSPECS score declined significantly from baseline (0) to follow-up (1) as well in Early Tx-group (from 7 to 5.7, ** $p<0.0042$) as in ATD group (ATD; from 7.35 to 5.9, ** $p<0.0033$), but with no significant differences between both cohorts ($p=0.56$). Data in **a** and **b** are shown as mean ± SEM. **c** Reduction of TRAb serum level (IU/l log). Serum TRAb activities declined significantly as well in Early Tx-group (from median 18.6 to 5.2, *** $p=0.0002$) as in ATD-group (from median 12.8 to 3.2, *** $p=0.0001$), but with no significant differences between both cohorts as calculated using Wilcoxon rank test ($p_0=0.07$, $p_{6months}=0.32$]. Data are shown as median with range.

(reviewed in [23,24]), and it has been shown, that consistent euthyroidism has a beneficial influence on the course of orbitopathy [25]. However, the effect of early thyroid ablation is still a matter of debate.

Ours is the first study to retrospectively assess the effect of early thyroidectomy on active, recently onset moderate to severe GO. We showed that early thyroidectomy after about 6 months of antithyroid treatment in GO-patients with low chance of remission did not influence final outcomes concerning remaining defects of GO in comparison to patients being further treated with thyreostatics. However, those patients benefit from early thyroidectomy, as they present with significantly less active GO and they show a significantly higher rate of inactivation of GO at 6 months follow-up. Our result is in line with reports from De Bellis et al. who reported on the effect of thyroidectomy at a later time point after 21–22 ± 9–11 months of antithyroid drug treatment [15]. Also, in this phase of the disease they observed a later and less marked improvement of GO in patients on methimazole treatment in comparison to patients that underwent thyroidectomy.

Concerning the treatment of hyperthyroidism, usually patients with GO and very low probability of remission (high TRAb, smokers, large goiter) have 2 options: long lasting antithyroid drug therapy or thyroidectomy. Radioiodine therapy is not the treatment of choice in smokers with high TRAb and moderate to severe active orbitopathy, as it carries a high risk of deteriorating orbitopathy [26]. Even after longtime antithyroid treatment, patients with persisting high serum activities of TRAbs have a higher risk of relapsing hyperthyroidism during any attempt to reduce the dose of thyreostatics, although this risk decreases slightly over time [27–29].

Total thyroidectomy, on the other hand, is associated with a low risk of relapsing thyroid disease and consecutive reactivation of orbitopathy (reviewed in [30]). Once thyroid hormone substitution is properly attuned and serum levels are within normal parameters, clinical follow-ups have to be performed only few times per year. Complications of thyroidectomy are relatively rare – these include transient recurrent laryngeal nerve palsies (1.3 % calculated on Nerves at Risk, NaR) or transient hypocalcaemia (approx. 7.4 %) [31]. Inactivation rates of GO can be increased if thyroidectomy is followed by a small dose radioiodine therapy called 'total ablation' [32,33], which nearly prevents recurrence of hyperthyroidism [34].

Therefore, lifelong hormone substitution vs. long term ATD have to be carefully evaluated in patients with low chance of remission. Early thyroidectomy should be considered preferably in patients who need to reach stable, inactive GO as quickly as possible, for example, patients with diplopia who need to drive, or women with the desire to have children.

The higher inactivation rate after early thyroidectomy shortens average active disease duration. Our examined cohort comprised mainly patients with moderate to severe GO – these are usually patients who do not go into remission [9]. Since these are largely patients who will undergo ophthalmosurgical repair of remaining defects, restorative functional and aesthetic oculoplastic surgery can be performed earlier in these patients. This consequently influences quality of life and especially the duration of sick leave of these patients with all associated socio-economic aspects.

Patients of the herein studied cohorts had already received extensive anti-inflammatory treatment prior to and during observation. We do not know, whether early thyroidectomy has an even greater impact on patients with untreated orbitopathy, in comparison to continuous thyreostatic treatment. This will be subject of a prospective randomized trial.

Table 2 Patient characteristics at follow-up.

Patients characteristics at follow-up	Early thyroidectomy group	p	ATD-Group
Smoker/Non-smoker (%)	60.9/39.1	0.5 ns	52.2/47.8
Duration of GD since initiation ATD (months) [a]	12 (10–14)	0.7 ns	12 (10–14)
Activity of GO (CAS score) [c]	2.1 ± 1.3	**0.02** *	2.8 ± 1.5
Patients with active/inactive GO (%) [b]	10.9/89.1		32.60/67.4
Inactivation rate (%)	89.1	**0.02** *	67.4
Severity of GO (NOSPECS score) [c]	5.7 ± 2.2	0.56 ns	5.9 ± 2.2
TRAb level [a]	5.2 (0.1–65.2)	0.32 ns	3.2 (0.1–53.1)
Anti-inflammatory therapy during observation period (%): Baseline until follow-up (No therapy/Steroids/Steroids and orbital irradiation)	22/26/52	0.8 ns	28/22/50
Protrusio: Hertel R/L pathological/normal (%) [d]	66.3/33.7	0.54 ns	60.9/39.1
Hertel difference between RE and LE (%) [e]	23.9/76.1	0.86 ns	21.7/78.3
Mean Edema Score (Injection/Chemosis/Swelling/Irritation)	5.1	0.38 ns	4.6
Mean Edema score pathological (≥ 2) (%)	45	0.03 *	38

[a] Data expressed as median (range)
[b] Active GO: CAS ≥ 4, Inactive GO: CAS < 4
[c] Data expressed as mean ± SD
[d] Hertel pathological (≥ 17 mm)/normal (< 17 mm)
[e] Hertel difference between Right Eye (RE) and Left Eye (LE) pathological (≥ 1.5 mm)/normal (< 1.5 mm)
* significant; ns: not significant

The immunological consequences of the removal of the thyroid have not been completely elucidated yet. Several lines of evidence suggest that the thyroid is a major site of autoantibody synthesis and antigen (Ag) presentation in the autoimmune thyroid diseases. Thyrocytes express HLA-DR [35] and CD40 [36,37] and may be involved in the induction of Graves' autoimmunity. The colocalization of thyrocytes, mature professional antigen-presenting cells and CD4+T-helper cells led to the extended concept that these cells might cooperatively stimulate thyroid autoimmunity [38,39]. IgG from patients with Graves` disease maintain the process since they induce Interleukin-16 and RANTES expression in cultured human thyrocytes: chemokines which modulate T cell activation [40]. And consequently, removal of the thyroid is followed by a continuous decrease of TRAb in most of the patients [11,41]. Takamura et al. showed even 100% TRAb elimination after total thyroidectomy in the long term follow-up of their cohort [42].

However, antithyroid drug treatment is also accompanied be a continuous TRAb decrease [41]. Methimazole treatment led to downregulation of major histocompatibility class II gene expression in FRTL-5 thyrocytes [43]. In experimental models of autoimmune uveitis methimazole inhibits uveitis at least in part by preventing the recruitment and/or maturation of antigen presenting cells, resulting in reduced generation of Ag-specific T cells [44]. However, since most of the patients are treated by titration regime the effect of total thyroidectomy on the autoimmune disease may outweigh the effect of low doses of thyreostatics and so be accompanied by a faster and more effective inactivation of GO.

Another aspect is epitope spreading. Although in general there is a close correlation between TRAb levels and the course of GO [45], there are patients with very high TRAb levels and no overt eye symptoms. Or there are patients who develop orbitopathy only later in the course with a relapse of thyroid hyperthyroidism. It has been shown that TSHR-Ab binding results in different signaling cascades. Stimulating antibodies use signaling pathways similar to the TSH activation. Both, TSH-blocking and neutral TSHR-antibodies, use other signaling networks which results

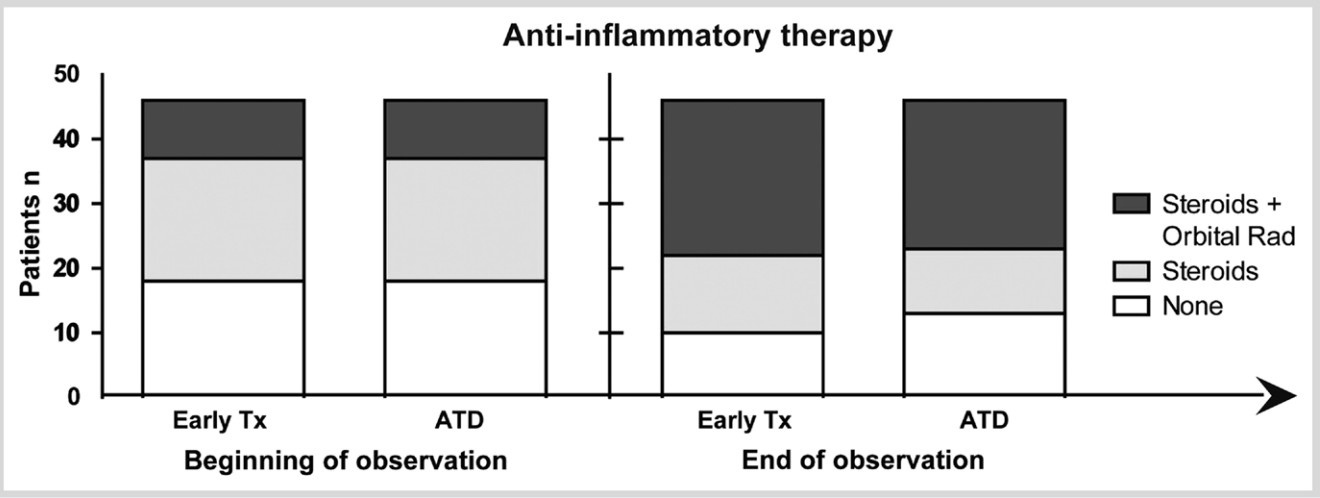

Fig. 2 Anti-inflammatory therapy (imt) of GO-patients before and during follow-up was comparable: At baseline, as well as at 12 m follow-up, patients in both groups had received comparable imt. At baseline, in each group, 9 patients had received steroids in combination with orbital irradiation, 19 patients had received steroids only, and 18 patients had had no imt at all (matched pairs) (p = 1). During follow-up, additional doses of steroids were given to 12 patients of the Tx-group and 10 patients of the ATD-group due to still active GO. Those who also had motility deficits, received steroids in combination with orbital irradiation: 24 (Tx-group) as well as 23 (ATD-group) (cumulative steroid doses remained < 4.5 g). Ten thyroidectomized patients vs. 13 in ATD-group had not required any further immunosuppressive treatment at the end of the observation period (p = 0.8).

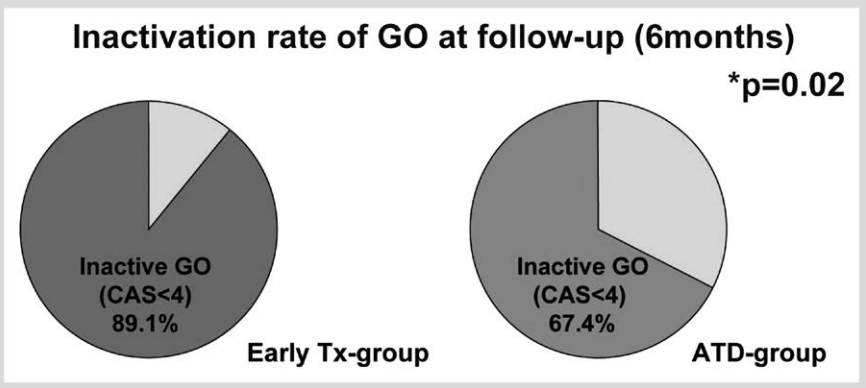

Fig. 3 Rate of inactivation: In the Early Tx-group, the inactivation rate was significantly higher than in ATD-group (* p = 0.02; calculated using Fisher's exact test). GO was considered as being active if CAS ≥ 4 and inactive if CAS < 4. In the Early Tx-group, from 46 cases of active GO at baseline, 41 were inactive after 6 ± 2 month follow-up (89.1 %). In the ATD-group, from 46 cases of active GO at baseline, 31 were inactive after 6 ± 2 month follow-up (67.4 %), while15 patients still presented with active GO.

in variable signal responses. For instance, via Gαq, the c-Raf-ERK-p90RSK signaling cascade is activated, while it is not activated by TSH [46,47]. For orbital fibroblasts it has been shown that signaling pathways of TSHR and the growth factor IGF1 influence each other (PKA and PI3K) with consequences for hyaluronan production [48]. These observations help to explain how TSHR-Abs may contribute to different clinical phenotypes.

Since there is clear evidence for Ag presentation in the thyroid, an early removal of the thyroid might prevent epitope spreading towards more antibodies specific for orbitopathy. Therefore, prevention of epitope spreading could be included in the list of arguments pro a definite therapy of the thyroid during the course of Graves' orbitopathy.

In conclusion, early thyroidectomy might be a good therapeutic option for patients with moderate to severe Graves' orbitopathy who have only low chances of remission. In this first, retrospective study, early thyroidectomy does not reduce remaining defects in comparison to antithyroid drug therapy. However, it speeds up inactivation of GO which may impact patients' sick leave and quality of life since rehabilitative surgery can be started earlier. To further study and define the effect of early thyroidectomy on the course and outcome of GO, future prospective randomized trials with large cohorts and without concomitant immunosuppressive therapy are necessary.

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Conflict of Interest

The authors declare no conflict of interest.

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