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Thyrotropin Receptor Autoantibodies Are Independent Risk Factors for Graves' Ophthalmopathy and Help to Predict Severity and Outcome of the Disease

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Objective: The objective of this study was to examine whether TSH-receptor antibody [TSH binding inhibitory antibodies (TBII)] levels are associated with the severity of Graves' ophthalmopathy (GO) over the entire course of the disease.

Methods and Patients: A total of 159 patients with GO were followed for 12–24 months. One year after the first symptoms of GO, all patients were classified into mild or severe GO according to their clinical manifestations. TBII were measured every 3 months after onset of GO. Receiver operating characteristic plot analysis was performed to assess the power to discriminate both patient groups by TBII (specificity >90%).

Results: TBII levels and prevalence at each time point during follow-up were significantly higher in patients with a severe course of GO compared with patients with a mild course of GO. Prognostic statements on the course of the disease were possible for about half of the GO patients at all time points (except the first). If at first presentation and at consecutive time points TBII levels were less than 5.7, 2.6, 1.5, 1.5, 1.5, and 1.5 IU/liter, the patients had a 2.3- to 15.6-fold higher chance of a mild course. If 5–8 months after GO onset and at consecutive time points TBII levels were above 8.8, 5.1, 4.8, 2.8, and 2.8 IU/liter, the patients had a 8.7- to 31.1-fold higher risk of a severe course. This relationship of TBII to the severity was independent from age and smoking.

Conclusion: Follow-up measurements of TBII allow, in half of the patients, assessment of the prognosis of GO and, therefore, could be of additional help for the disease management. **(*J Clin Endocrinol Metab* 91: 3464–3470, 2006)**

GRAVES' OPHTHALMOPATHY (GO) is clinically associated with autoimmune thyroid disease, but the precise pathophysiological link is still under debate (1). Over the last few years, there was increasing evidence for common autoantigens between the thyroid and the orbita. Pathophysiological relevance of these antigens for GO was supplied by the demonstration of TSH-receptor (TSH-R) transcripts (2–5) and thyroglobulin in its native conformation (6, 7) in the orbital tissue from GO patients.

Autoantibodies to thyroidal antigens, particularly TSH-R autoantibodies (TRAb), might be involved in the disease process of GO, and their detection may be of clinical benefit. A number of experimental and clinical studies support the theory of TRAb involvement in GO (8–15). One study in an Asian population (12) reported an increase in the prevalence of GO with increasing thyroid stimulating antibodies. This was confirmed independently in a similar ethnic background (13). In a euthyroid Caucasian population, GO activity and proptosis were mainly associated with the TRAb fraction of TSH binding inhibitory antibodies (TBII) (14).

Although the role of TRAb in GO is now accepted by many researchers and clinicians, their use in the disease management of GO is less well studied than the role of TRAb for the diagnosis and therapy monitoring of Graves' disease. In GO, the clinical problem is not the diagnosis of the disease, because this is pretty obvious from the clinical presentation, but the treatment of the eye symptoms in the individual patient. In general, the treatment of choice is oral or iv steroids, which have well-known side effects. The purpose of this antiinflammatory treatment is the prevention of further deterioration and the improvement of marked disease. The decision for steroid treatment or irradiation is based on objective findings of detailed ophthalmological examination. However, it is known that the natural course of GO is benign in a considerable proportion of patients (16), and so some patients might improve without therapy, whereas the initial choice of steroid dosage may be too low in patients with a severe course. Other challenges in the clinical routine include the decision to continue or stop antiinflammatory therapy in patients with mild but persisting inflammation, and the definition of the right moment for surgical rehabilitation (because surgery should not be performed if the patient is still at risk for further deterioration). These clinical decisions are often difficult, and it would be valuable for the ophthalmol-

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Abbreviations: ATD, Antithyroid drug; AUC, area under the curve; CAS, clinical activity score; GO, Graves' ophthalmopathy; ROC, receiver operating characteristic; TBII, TSH binding inhibitory antibodies; TRAb, TSH-receptor autoantibody; TSH-R, TSH-receptor.

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ogist, if he had risk factors for the prediction of the course of GO. So far, only a few risk factors are discussed, among them, the kind and the effect thyroid treatment (17) and smoking (18, 19).

Recently, we could show that TRAb titers and prevalence correlate with the severity and activity of GO even after the end of antiinflammatory therapy (15). This observation was probably made possible with a second-generation assay for TRAb detection (20), which allows a longer follow-up of autoantibodies in patients with Graves' disease (21, 22) and even the detection of TRAb in GO patients without hyperthyroidism (11).

However, the association and potential predictive value of TRAb during the entire clinical course of GO has not yet been demonstrated. In this observational study, we wanted to examine whether TRAb levels are associated with the severity of GO over the entire course of the disease.

Patients and Methods

Patients

A total of 159 patients were included in the study. Clinical data were recorded at six time points within 1–4, 5–8, 9–12, 13–16, 17–20, and 21–24 months after onset of GO. Of these patients, 92 were followed from the first time point, another 29 from the second time point, and another 38 from the third time point onward. All patients were seen at least at three time points and over at least 12 months.

Of all patients, 69 (43.3%) developed GO at the same time as hyperthyroidism or had symptoms of GO even before the onset of thyroid disease, 80 patients (50.3%) developed GO months to years after the onset of hyperthyroidism [of these, 54 patients were under treatment with antithyroid drugs (ATD) or developed GO together with a relapse of hyperthyroidism after cessation of ATD therapy, and 26 had undergone thyroidectomy or radioiodine therapy before the onset of GO]. Two patients (1.2%) had autoimmune thyroiditis at GO onset, whereas eight (5.0%) had no underlying thyroid disease at all.

During follow-up, all patients with clinical activity score (CAS) values greater than 2 were offered to be treated with steroids. For mild and moderate disease, an oral regime beginning with 1.5 mg fluorocortolone per milligram of body weight was delivered. The dosage was tapered by 10 mg every 4 d. For severe disease, iv steroids were given (on 3 of 5 d, a single dose of 500 mg Soludecortin H per day; each treatment day followed by a therapy-free day), and this treatment was followed by the same oral regime as described above. Orbital irradiation was initiated when the patients had impairment of motility and when clinical activity increased again after withdrawal of steroids.

Hyperthyroidism was treated with ATD for 1 yr. In case of relapse of hyperthyroidism, patients were assigned to radioiodine therapy, thyroidectomy, or another cycle of ATD for 1 yr, according to the preference of the patient. Remission was defined as at least 6 months of euthyroidism after cessation of ATD therapy.

All patients were examined by the same clinician at every visit, who was blinded for the TRAb data and who assessed the following ophthalmological parameters: visual acuity, lid width, downward movement of the lids (in millimeters), proptosis (in millimeters), inflammatory signs (redness and swelling of lids and conjunctiva), and eye motility (monocular excursions measured with the Kestenbaum glasses). In case of reduced visual acuity, the cornea was stained with fluoresceine, and if slit lamp and fundus examination revealed normal anatomical conditions, visual evoked potentials were done to examine optic nerve function.

The CAS of GO was estimated according to Mourits *et al.* (23). The severity of eye disease was estimated with a modified NOSPECS classification as described in Table 1.

TRAb assay

Serum taken at all six time points was collected and frozen. TRAb were measured in batches every 6 months with a second-generation TBII assay based on the human recombinant TSH-R (20) (TRAK human LIA; B.R.A.H.M.S AG, Hennigsdorf/Berlin, Germany). This assay is calibrated in international units, based on the World Health Organization reference standard MRC 90/672. The 50% inhibition of tracer binding corresponds to 7–8 IU/liter. Values equal to or greater than 1.5 IU/liter (about 10% tracer binding) were regarded as positive, values between 1–1.5 IU/liter were regarded as borderline, and values less than 1.0 IU/liter were regarded as negative as described in detail elsewhere (24).

Grouping of patients

At 11–14 months follow-up, patients were grouped as those with a mild course or with a severe course of GO. This was done on the basis of the clinical activity and severity of GO as follows: mild course, CAS less than 4 (almost inactive disease) and NOSPECS less than 5 (mild symptoms of GO); severe course, CAS equal to or greater than 4 (still active disease) and/or NOSPECS equal to or greater than 5 (marked symptoms of GO). The examiner who classified the patients was blinded for TRAb values.

Statistical analysis

Antibody levels between groups were compared by the Mann-Whitney *U* test. Raw data were also transformed into dichotomous values of elevation (yes/no) and displayed in histograms with binominal 95% confidence intervals. Both groups were tested for statistical difference with Fisher's exact test.

Receiver operating characteristic (ROC) plot analysis was performed to find out whether it is possible to predict a severe course or a good course of GO at certain cutoff levels of TBII. To define cutoffs for the prediction of a severe prognosis, sensitivity was calculated from patients with severe GO and specificity from patients with mild GO. Inverse data sets were used to define cutoffs for a good prognosis. Negative predictive values (for the good prognosis) and positive predictive values (for the bad prognosis) and odds ratios were calculated with two-by-two tables.

Multivariable logistic regression was performed to investigate the influence of TBII on the course of GO in addition to age, gender, thyroid function, thyroid treatment, and smoking.

TABLE 1. Modified NOSPECS score to define disease severity

	NOSPECS score			
	0	1	2	3
Lid retraction	No	Yes		
Soft tissue inflammation[a]	0	1–4	5–8	>8
Proptosis	<17 mm	17–18 mm	19–22 mm	>22 mm
Site difference	<1 mm	1–2 mm	3–4 mm	>4 mm
Extraocular muscle involvement	No		>20° upgaze, >35° abduction	≤20° upgaze, ≤35° abduction
Corneal defects	No	Yes		
Optic nerve compression	No			Yes

[a] Upper lid edema, 0–2; lower lid edema, 0–2; conjunctival injection, 1; and conjunctival chemosis, 1.

Results

Clinical results

A total of 159 patients were followed up over 12–24 months after their initial clinical presentation with GO. Seventy-three patients passed the last time point after 24 months. The clinical presentation was assessed every 3–4 months by the same physician using the CAS and NOSPECS score. After 12 months of follow-up, 74 patients (47%) could be attributed to a mild course of GO, whereas 85 patients (53%) had a severe course of the disease.

The median duration of thyroid disease at GO onset in the group with a mild course was 0 months (ranging from 21 yr before onset to 10 months after the onset of GO), and 2.4 months in the group with a severe course (ranging from 30 yr before onset to 8 months after the onset of GO). Among the patients were 137 females (66 with mild course, 71 with severe course) and 22 males (eight with mild course, 14 with severe course). Smokers were more prevalent (37 with mild course, 54 with severe course) than nonsmokers (37 with mild course, 31 with severe course). The mean ages of patients with a mild and severe course were 44 yr (range 24–72) and 50 yr (range 24–83), respectively.

Steroids were given to 53 of 74 patients (71.6%) with mild course of GO and to 80 of 85 patients (94%) with severe course (contraindications prevented steroid treatment in five patients with severe GO, who would have been treated otherwise). Irradiation was applied to 23 of 74 patients (31.0%) with mild course and to 67 of 85 patients (78.8%) with severe course of GO. Patients with severe GO received significantly more antiinflammatory treatment than patients with mild GO ($P < 0.001$).

Within the observation period, 130 of 159 patients (60 with mild course, 70 with severe course of GO) had received definitive treatment of the thyroid, or completed a period of 6 months after the cessation of ATD therapy, or were euthyroid the whole period or had Hashimoto's thyroiditis and were substituted with L-thyroxine. The remaining 29 had not yet finished 6 months after cessation of ATD therapy or had not yet received ATD. Of the patients with severe course of GO, 61 of 70 (87%) had received definitive treatment of the thyroid [of those, 38 (54%) underwent thyroidectomy, 13 (18%) underwent radioiodine treatment, 10 (14%) underwent thyroidectomy and radioiodine], six (9%) received another cycle of ATD, and only one patient (1.4%) was in remission after 2 yr. In comparison, from the patients with mild course of GO, only 24 of 60 (40% $P < 0.0001$ *vs.* severe course) had received definitive treatment [19 (32%) received thyroidectomy, four (6.7%) received radioiodine treatment, one (1.7%) received thyroidectomy and radioiodine]. Another five patients (8%) received another cycle of ATD, and 23 (38%) went into remission. Among the rest of the patients were two with Hashimoto's thyroiditis (both mild course) and eight (six mild course, two severe course) who were still euthyroid and had never received ATD.

TBII levels of patients with mild and severe GO

At each time point during follow-up, median TBII levels were significantly higher in patients with severe course of GO in comparison to patients with mild course of GO. Median TBII levels in GO with severe course were 19.0 IU/liter at the first visit and 13.2, 7.7, 6.2, 6.6, and 5.8 IU/liter during subsequent follow-ups (Table 2 and Fig. 1B). In the group of GO patients with mild course, the respective TBII values were 5.2 IU/liter at the first visit, and 2.2, 1.1, 1.0, 0.1, and 0.5 IU/liter during follow-ups (Table 2 and Fig. 1A).

TABLE 2. TBII values (median) over 2 yr of patients with a mild and a severe course of GO

Time point: months after GO onset	Mild course of GO (median) TBII (IU/liter)	Severe course of GO (median) TBII (IU/liter)	*P* value
1–4	5.2	19.0	0.0001
5–8	2.2	13.2	<0.0001
9–12	1.1	7.7	<0.0006
13–16	1.0	6.2	<0.0001
17–20	0.1	6.6	<0.0001
21–24	0.5	5.8	<0.0001

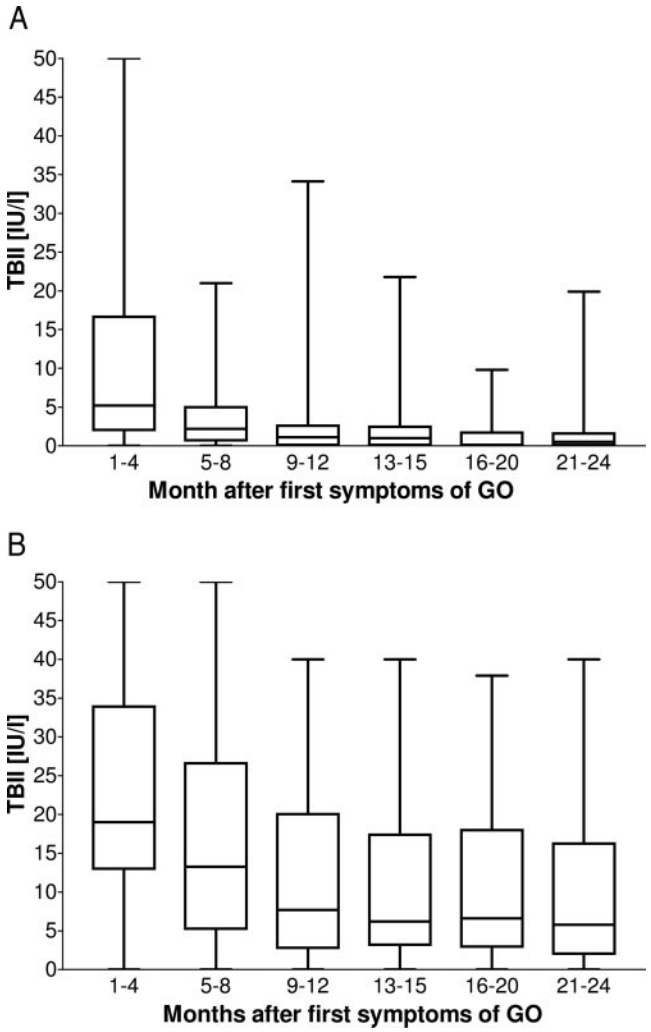

FIG. 1. Association between the level of TRAb and the severity of GO. TRAb were determined by a TBII assay calibrated in international units (international units per liter), where 7–8 IU/liter correspond to 50% inhibition of tracer binding. Shown are median (*line*), interquartile range (*box*), and total range (*whiskers*) for TBII levels over a 2-yr follow-up period of patients with mild course of GO (A) and patients with a severe course of GO (B). TBII levels were significantly (see Table 2 for *P* values) different at all time points during follow-up.

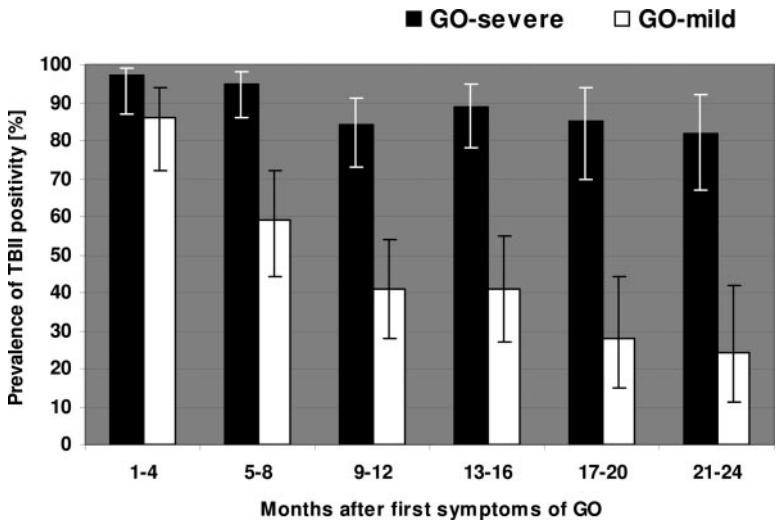

FIG. 2. Association between the prevalence of TRAb and the severity of GO. TRAb were determined by a TBII assay. Shown is the TBII prevalence of patients with mild (*white bars*) and severe course of GO (*black bars*) over a 2-yr follow-up of the disease.

Prevalence of TBII in patients with mild and severe GO

At the first time point, TBII levels were positive in 97% of the patients with severe course in comparison to 86% in the patients with mild course of GO. This difference was not significant ($P = 0.61$). However, the prevalence of TBII declined significantly faster in the patients with mild course in comparison to patients with severe course of GO. One year after the first signs of GO, the prevalence of TBII was still 83% in the group of patients with severe course but only 40% in the group of patients with mild course of GO ($P < 0.0001$). After 2 yr, this difference was even more prominent, with only 24% of patients positive with mild course compared with 82% with severe course ($P < 0.0001$) (Fig. 2).

Calculation of cutoff TBII values by ROC plot analysis

Both groups showed significant differences in their TBII levels (Table 2). ROC plot analysis was performed to find out whether this difference was relevant enough to define TBII cutoff levels at which a mild or severe course of GO could be predicted. Except for the first time point [area under the curve (AUC) 0.75, $P < 0.001$], the ROC plot AUCs were always between 0.82 and 0.87 ($P < 0.001$ for all). A specificity of at least 90% was selected to define TBII cutoff levels for the prediction of a mild or severe course of GO. For those chosen cutoff levels, negative and positive predictive values and the corresponding odds ratios were calculated. All data are shown in Tables 3 and 4 and Fig. 3.

Prognostic statements on the course of the disease were possible at all time points (except one). If at first presentation and at consecutive time points TBII levels were less than 5.7, 2.6, 1.5, 1.5, 1.5, and 1.5 IU/liter, the patients had a 2.3- to 15.6-fold higher chance of a mild course. If 5–8 month after GO onset and at consecutive time points TBII levels were above 8.8, 5.1, 4.8, 2.8, and 2.8 IU/liter, the patients had an 8.7 to 31.1 times higher risk of a severe course. Within the first 4 months, prediction was only possible for a mild course, but not for a severe course, because at this early and active phase of the disease, high TBII levels occurred also in patients with mild GO.

Also, prognostic statements on the basis of TBII levels were only possible for about half the patients in the first year after onset of GO. The other half had TBII levels in a sort of "gray zone" where no reasonable and clinically helpful risk assessment was possible. Exact patient numbers for every time point are given in Tables 3 and 4.

Influence of different risk factors on the course of GO

For the time point 5–8 month after onset of GO (which is probably most relevant for clinical decisions), a multivariable logistic regression was performed to investigate the influence of TBII on the course of GO in addition to age, gender, thyroid function, thyroid treatment, and smoking. This regression analysis revealed that TBII ($P = 0.0005$), smoking behavior ($P = 0.0048$), and age ($P = 0.0002$) all have significant influence on the course of GO. The risk ratio of 1.27 for TBII means that, with an increase of 1 IU/liter, the risk to

TABLE 3. TBII cutoff levels for the prediction of a mild course of GO at a specificity level of 90%

Time point: months after GO onset	TBII cutoff (IU/liter)	Sensitivity (%)	Negative predictive value	Odds ratio	Patients in the gray zone (see Fig. 3)/all patients (fat)
1–4	5.7	51	0.89	13.9	24/49
5–8	2.6	56.9	0.78	6.8	28/51
9–12	1.5	57.6	0.7	3.7	25/59
13–16	1.5	61.2	0.84	15.6	19/49
17–20	1.5	64	0.7	2.3	14/39
21–24	1.5	70	0.78	14.7	10/33

Corresponding sensitivity values from the ROC plot analysis and negative predictive values and corresponding odd ratios are given. Example: a GO patient presenting at 1–4 months after onset of the disease with TBII values below 5.7 IU/liter has a 13.9-fold higher chance of a mild course of GO than a patient with TBII values above this cutoff.

TABLE 4. TBII cutoff levels for the prediction of a severe course of GO at a specificity level of 90%

Time point: months after GO onset	TBII cutoff (IU/liter)	Sensitivity (%)	Positive predictive value	Odds ratio	Patients in the grey zone (see Fig. 3)/all patients (fat)
1–4	–	–	–	–	–
5–8	8.8	66.7	0.88	18.4	20/60
9–12	5.1	65.7	0.88	16.9	24/70
13–16	4.8	61.9	0.88	14.3	24/63
17–20	2.8	78	0.88	31.1	9/41
21–24	2.8	62	0.82	8.7	15/40

Corresponding sensitivity values from the ROC plot analysis and positive predictive values and corresponding odd ratios are given. Example: a GO patient presenting at 5–8 months after onset of the disease with TBII values above 8.8 IU/liter has a 18.4-fold higher risk of a severe course of GO than a patient with TBII values below this cutoff. –, There is no prediction at the 1–4 time point.

develop a severe course of GO is 1.27-fold (or 27%) higher. The results for gender ($P = 0.078$) and the type of thyroid treatment ($P = 0.075$) revealed a trend but were not significant. The actual free T_4 levels at time point 5–8 months after GO onset ($P = 0.96$) had no independent impact on the course of GO. All data are shown in Table 5.

Discussion

Clinical decisions in the long-term treatment of patients with GO are sometimes difficult. Despite clinical examination and standard treatment regimens, if in doubt, ophthalmologists have no real GO outcome prediction or therapy stratification marker. Although there is increasing evidence that disturbed thyroid function and "risk factors" like smoking have a negative effect, these parameters have yet little practical value. In this context, the role of TRAb has not yet been examined during the follow-up of patients with GO. In this study, we looked at GO patients who were followed over 2 yr and were grouped into mild or severe course of GO. Both groups differ from each other significantly with respect to TRAb levels and prevalence. This difference was evident over the entire 2-yr follow-up period.

These results support the role of TRAb in the pathogenesis of GO. The fact that higher TRAb titers and prevalence were present in patients with more severe GO over the entire course of the disease suggests that TRAb not only trigger but also constantly maintain the autoimmune process in the orbita. This clinical observation is in accordance with *in vitro* studies. Expression of TSH-R is augmented in orbital tissues from patients with GO and in newly differentiated adipocytes derived from precursor cells taken from the orbit (reviewed in Ref. 25). Recently it could be shown that TSH-R expression in orbital fat/connective tissue can be related to the CAS (26).

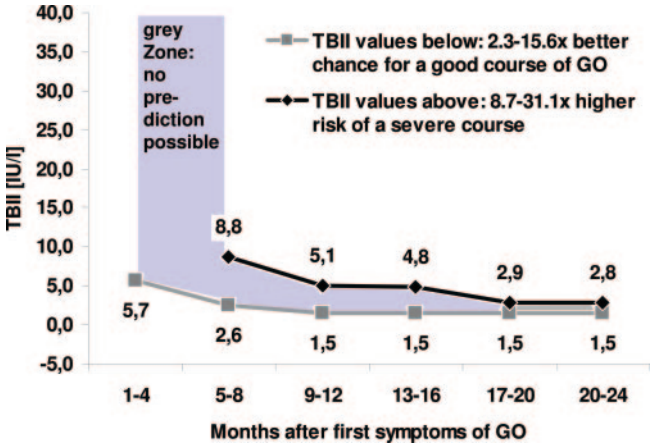

FIG. 3. Cutoff TBII levels for the prediction of a good course of GO (*gray line*) and for the prediction of a bad course of GO (*black line*). For patients with a TBII level within the *gray zone*, no prognostic statement for the course of their GO is possible.

Although this observational difference is certainly interesting, the clinically relevant question has to be: were these differences of TRAb levels between patients with mild and severe GO substantial enough to recognize patients at low or high risk for severe course at certain cutoff levels with high specificity? ROC plot analysis revealed that prognostic decisions were possible at nearly all time points of the disease for about half of the patients. Cutoff TBII levels for a good prognosis could be defined at every time point of the disease. Cutoff TBII levels for a bad prognosis were not available in the first 4 months of the disease, but were available at every time point afterward. The calculated AUC for these time points were between 0.82 and 0.87, which is smaller than the AUC for the diagnosis of Graves' disease (20), but superior or comparable to well-established clinical routine procedures like Papanicolaou smear (AUC 0.70) or mammography (AUC 0.85) (27, 28).

As mentioned, there are only a few clues for the ophthalmologist to estimate the course of GO, like thyroid function (29, 30), TSH stimulation during disease (31), radioiodine therapy (32, 33), and smoking (18, 19). Therefore, it is very helpful to have, in addition to objective findings on detailed ophthalmological examination, a serum marker, which can be easily monitored during the follow-up. Patients with TRAb levels above a certain cutoff indicating a severe course of GO could benefit from a modified or prolonged immunosuppressive therapy and shorter control intervals. On the

TABLE 5. Multiple logistic regression analysis of factors with influence on the course of GO at time point 5–8 months after onset of GO

Risk factor	*P* value	Risk ratio (95% CI)
TBII level (1 IU/liter increase)	0.0005	1.27 (1.11–1.46)
Smoking behavior (yes/no)	0.0048	9.03 (1.96–41.71)
Age (1 yr increase)	0.0002	1.14 (1.07–1.23)
Sex	0.0787	5.39 (0.82–35.2)
Type of thyroid treatment	0.0751	1.74 (0.94–3.22)
Free T_4 level	0.961	0.96 (0.86–1.07)

The risk ratio of 1.27 for TBII means that, with a TBII increase of 1 IU/liter, the risk of a severe course is 1.27 times (27%) higher.

other hand, for patients with low or undetectable TRAb, a conservative approach (wait and see) could be justified, and the long-term results of ATD treatment alone could be sufficient without further need for steroids. But these hypotheses certainly have to be proven in prospective interventional clinical trials.

The follow-up also revealed that patients with a mild course of GO had a better prognosis for their thyroid disease. The presence of ophthalmopathy is known as a risk factor that increases the rate for relapses of hyperthyroidism (reviewed in Ref. 34). In our cohort, only 1.4% of the patients with a severe course of GO went into remission in comparison to 38% of the patients with a mild course of GO.

This possible usefulness of TRAb in the management of GO has not been suggested so far, because early studies questioned the role of TRAb in the disease process. This inconclusive picture was probably due to difficult patient classification and low sensitivity of assay systems (reviewed in Ref. 14). Several recent clinical and experimental studies applying more stringent selection criteria found evidence to support the theory of autoantibody involvement in GO (12–14). Another long-term follow-up study after iv steroid therapy of GO patients was unable to show an association of TRAb level to response or nonresponse to the therapy. However, the first-generation TRAb assay used in this study has a lower sensitivity (35) and might not have been suitable to detect differences.

A limitation of our study is the observation that TRAb levels of half of the patients were in an intermediate gray zone with a low predictive value. This partly is due to the grouping of the patients, because both groups contain patients with moderate GO (some of whom improved, others did not). Another reason is the heterogeneous treatment of hyperthyroidism in our patient cohort. TRAb levels usually decline after the beginning of ATD therapy or thyroidectomy (21, 36, 37) but increase dramatically after radioiodine therapy (38). In addition, more smokers were present in the group with severe GO, and it is well described that smokers develop a more severe GO than nonsmokers (39, 40). Nevertheless, we show in this study that the described association of TRAb to the course of GO is independent from smoking behavior and age.

Conclusion

Follow-up measurements of TRAb allow, in half of the patients, assessment of the prognosis of GO. This study was designed as observational, and the clinical usefulness of the described association between TRAb levels and course of GO has to be proven in prospective interventional studies.

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