

Predictive score for the development or progression of Graves' orbitopathy in patients with newly diagnosed Graves' hyperthyroidism

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Abstract

Objective: To construct a predictive score for the development or progression of Graves' orbitopathy (GO) in Graves' hyperthyroidism (GH).

Design: Prospective observational study in patients with newly diagnosed GH, treated with antithyroid drugs (ATD) for 18 months at ten participating centers from EUGOGO in 8 European countries.

Methods: 348 patients were included with untreated GH but without obvious GO. Mixed effects logistic regression was used to determine the best predictors. A predictive score (called PREDIGO) was constructed.

Results: GO occurred in 15% (mild in 13% and moderate to severe in 2%), predominantly at 6–12 months after start of ATD. Independent baseline determinants for the development of GO were clinical activity score (assigned 5 points if score > 0), TSH-binding inhibitory immunoglobulins (2 points if TBII 2–10 U/L, 5 points if TBII > 10 U/L), duration of hyperthyroid symptoms (1 point if 1–4 months, 3 points if > 4 months) and smoking (2 points if current smoker). Based on the odds ratio of each of these four determinants, a quantitative predictive score (called PREDIGO) was constructed ranging from 0 to 15 with higher scores denoting higher risk; positive and negative predictive values were 0.28 (95% CI 0.20–0.37) and 0.91 (95% CI 0.87–0.94) respectively.

Conclusions: In patients without GO at diagnosis, 15% will develop GO (13% mild, 2% moderate to severe) during subsequent treatment with ATD for 18 months. A predictive score called PREDIGO composed of four baseline determinants was better in predicting those patients who will not develop obvious GO than who will.

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Introduction

A subset of patients with Graves' hyperthyroidism (GH) also have Graves' orbitopathy (GO) (1). Development of GO is feared by patients because it substantially impairs quality of life due to interference with visual functions and unmistakable changes in appearance (2). Fortunately, not all patients with Graves' disease develop GO. At the time of diagnosing GH, about 75% have no GO (3). However, GO may become evident after starting treatment for hyperthyroidism. In patients with newly diagnosed GH presenting without obvious GO, it might be useful if one could estimate the risk of developing GO. In patients with sufficiently high risk, one may prefer treatment with antithyroid drugs or total thyroidectomy rather than radioactive iodine in view of the adverse effect of ¹³¹I on the course of GO (4, 5, 6). In high-risk patients, one could also envisage prophylactic treatment with selenium, which does prevent worsening of GO in mild cases (7). Therefore, a prospective study was initiated in patients with newly diagnosed GH without overt GO, aiming at constructing a predictive score for developing GO during antithyroid drug treatment. Well-known risk factors for GO are smoking (8) and high serum concentrations of TSH receptor antibodies (9, 10). Age, gender and thyroid function were also evaluated as putative predictors, because older age, male sex and biochemically severe hyperthyroidism have all been associated with more severe GO (5, 11, 12).

Patients with overt GO were excluded, but mild eyelid swelling and mild conjunctival redness were no reason to exclude patients. The rationale behind this is that minimal swelling and redness of the eyes in the absence of other ophthalmological signs compatible with GO are not necessarily diagnostic of GO: some swelling and redness of the eyes are common in many subjects regardless of Graves' disease. Thus, minimal swelling and redness in our study participants at baseline was considered as either a finding unrelated to the diagnosis of Graves' disease, or representing very mild, almost subclinical GO. However, the presence of even minimal swelling and redness score 2 points on the clinical activity score (CAS), a widely used tool to assess activity of GO (13). That score by itself should not be taken as evidence for the existence of GO as it should be realized that the CAS is not specific for the diagnosis of GO. Any inflammatory eye or orbital disease may result in swollen, red or painful eyes, and thus, in positive CAS scores. Therefore, it was decided to include the evaluation of baseline CAS as a putative

predictor of developing GO. Furthermore, the predictive value of the Vancouver Orbitopathy Rule was assessed, a short questionnaire for self-reporting of GO symptoms in patients with a recent diagnosis of GH (14).

Subjects and methods

Patient recruitment

Patients were recruited from ten participating centers of the European Group on Graves' Orbitopathy (EUGOGO) in the period May 2009–May 2014. Inclusion criteria were untreated GH, absence of overt GO and planned treatment with antithyroid drugs for 18 months. Definition of GH was (a) decreased TSH, elevated FT4 and/or FT3 and (b) diffusely enlarged thyroid gland (either by palpation or ultrasonography) and/or homogeneous thyroid uptake at scintigraphy. Antithyroid drugs could be administered according to either the titration method or the block-and-replace regimen, in line with standard policies of each participating center.

The mere presence of mild conjunctival redness and/or mild eyelid swelling (according to Figs 6 and 7 respectively in the color atlas by Dickinson and Perros) (15) was not a reason to exclude patients, provided other signs suggesting GO were absent. Exclusion criteria were (1) previous or planned treatment with ¹³¹I or thyroidectomy, (2) presence of GO, defined as one or more of the following eye changes: (a) soft tissue changes (moderate or severe eyelid/conjunctival redness, moderate or severe eyelid/periorbital swelling) as depicted in the color atlas (15); (b) proptosis above the upper normal limit (Asians 18 mm, Caucasians 20 mm, blacks 22 mm); (c) diplopia (intermittent, inconstant or constant); (d) decreased visual acuity attributable to GO, (3) drugs interfering with natural course of GO (e.g. steroids, cytokines, anticytokines, thiazolidinediones, selenium), (4) drugs interfering with thyroid function (e.g. amiodarone, lithium, iodine supplements), (5) drug or alcohol abuse, (6) no informed consent.

Approval of institutional review boards or local ethical committees was not deemed necessary because the study protocol did not require additional procedures beyond those done in the delivery of usual care. Nevertheless, consent has been obtained from each patient after full explanation of the purpose and nature of all procedures.

Putative determinants

Putative determinants for developing GO were assessed at baseline before starting antithyroid drugs. They included age and gender, family history of autoimmune thyroid disease, other autoimmune diseases in the patient, duration of hyperthyroid symptoms until start of antithyroid drugs, biochemical severity of hyperthyroidism (TSH, FT4, FT3), immunological severity (TBII, TPOAb), smoking behavior (never smoker, ex-smoker, current smoker), CAS and the Vancouver Orbitopathy Rule (14). The Vancouver Orbitopathy Rule consists of five questions: (1) do you have redness in your eyes or eyelids? (2) do you have swelling or feeling of fullness in one or both of your upper eyelids, (3) do you have bags under the eyes? (4) do your eyes seem to be too wide open? (5) is your vision blurry, even with glasses/contacts? If answers to questions 2 or 3 was 'yes' and in addition if any of the answers 1, 4 or 5 was 'yes', the result is labeled positive (sensitivity 0.76 and specificity 0.82 for the diagnosis of GO in patients with GH) (14).

Study protocol

In this prospective cohort study, baseline assessment of eye changes and putative determinants were performed mostly by endocrinologists. Soft tissue changes were recorded according to the color atlas (15), lid aperture in mm in midline by ruler, proptosis in mm by Hertel exophthalmometer; CAS scores were at a scale from 0 to 7 (13). Patients were asked about double vision (none, intermittent, inconstant, or constant), decreased visual acuity and disturbed color vision (if present, patient was referred to the ophthalmologist). Antithyroid drugs were started after blood sampling.

Follow-up visits at 6–12–18 months included blood sampling and re-assessment of smoking behavior and eye changes, again by the endocrinologist.

End-points of study were development of GO as defined under exclusion criterion 2 (GO was also diagnosed if proptosis values had increased by more than 2 mm) or otherwise at 18 months when antithyroid drugs were discontinued. Premature stops could happen if 131I therapy or thyroidectomy was performed earlier than 18 months or in case of severe intercurrent illness. Discontinuation of antithyroid drugs before 18 months or pregnancy ($n=2$) were no reason to exclude patients.

Statistical analysis

Assays of thyroid function and thyroid antibodies were done at each center in the local laboratory. As different

assays with different reference values were used, all obtained results were standardized by dividing obtained results by the upper normal limit of that assay, and then multiplied by the most common upper limit of the reference range. Normally distributed data are reported as mean $\pm$ s.d., while data not normally distributed are reported as median with range. Categorical variables are recorded as numbers and percentage. TBII was measured by second generation assays.

The objective of the statistical analysis was to identify determinants of developing GO and to construct a predictive score (called PREDIGO). Comparisons were made between patients who did or did not develop GO during the 18-month follow-up period. Odds ratios for developing GO were calculated for each of the putative determinants assessed at baseline, using univariate logistic regression. For multivariate analysis, mixed effects logistic regression was performed to find which factors were independently related to GO. R and lme4 software were used (16, 17). As fixed effects, clinical, laboratory and demographic data were entered, and as a random effect intercept for center. Because of the wide distribution of the data, logarithmic transformations for TSH, FT4, TPOAb, TBII and duration of hyperthyroid symptoms were used. To find the optimal model, multiple models were created and compared. *P* values were obtained by likelihood ratio tests of the model with the effect in question against the model without the effect in question. 95% confidence intervals for effects were calculated using the Wald method. For the predictive score, significant parameters were used as obtained by the logistic regression. Number of score points assigned to each parameter was calculated using the Framingham method (18). The sum of the score points constituted the PREDIGO score. Optimal cut-off for the PREDIGO score was obtained by analysis of the ROC curve and minimizing distance between ROC plot and point (0, 1) (19). The characteristic of the predictive score was assessed by bootstrapping.

Results

392 patients were recruited. Eleven patients were subsequently excluded (9 opted for thyroidectomy and 1 for radioactive iodine, and 1 patient suffered a stroke). Another 33 patients were lost to follow-up, leaving 348 patients for analysis. Characteristics of the study population are listed in Table 1. Two patients became pregnant during the study period; one of them

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Table 1 Baseline characteristics of 348 patients with Graves' hyperthyroidism treated with antithyroid drugs for 18 months: 295 patients remained without GO and 53 patients developed GO during 18 months of follow-up.

	348 patients	295 patients without GO group A (85%)	53 patients with new GO group B (15%)	P value (A vs B)
Age [†]	42.9 ± 13.2 year	42.4 ± 13.1 year	45.7 ± 13.1 year	0.087
Female/male gender	82%/18%	84%/16%	75%/25%	0.169
Caucasian/other ethnicity	94%/6%	93%/7%	96%/4%	0.550
Family history of AITD	20%	19%	26%	0.321
Other AI disease in patient	6%	6%	4%	0.750
Never/ex/current smokers	58%/13%/29%	60%/14%/26%	43%/8%/49%	0.002
Pack-years*	15 (7.5–24)	15 (7.3–22.9)	20 (15.5–32.5)	0.051
Cigarettes/day [†]	12.7 ± 7.0	11.5 ± 5.9	16.0 ± 8.6	0.022
Duration of symptoms months ^{§,*}	3 (1.5–5.25)	3 (1–5)	4 (2–6.25)	0.007
Antithyroid drugs: titration/block-and-replace	80%/20%	80%/20%	88%/12%	0.179
TSH (U/L)*	0.01 (0.00–0.02)	0.01 (0.00–0.02)	0.01 (0.00–0.02)	0.463
FT4 (pmol/L)*	36.6 (27.2–51.5)	36.4 (27.1–50.2)	39.4 (29.4–59.4)	0.102
FT3 (pmol/L)*	13.6 (8.2–22.1)	13.6 (8.1–22.0)	13.3 (8.6–23.1)	0.689
TPO (kU/L)*	200 (46–1000)	206 (47–1060)	164 (17–600)	0.141
TBII (U/L)*	6.8 (3.8–13.4)	6.4 (3.7–12.8)	11.0 (5.1–21.5)	0.006
CAS score (0/1/2)	89%/10%/<1%	92%/7%/<1%	73%/25%/2%	<0.001
Vancouver Orbitopathy Rule negative/positive	98%/2%	99%/1%	94%/6%	0.075
Lid aperture (mm) [†]	9.5 ± 1.7	9.5 ± 1.8	9.6 ± 1.7	0.806
Proptosis (mm) [†]	16.9 ± 2.2	16.8 ± 2.2	17.3 ± 2.2	0.028

[§]Hyperthyroid symptoms until start of antithyroid drugs; [†]mean ± s.d.; *median values with interquartile range. AI, autoimmune; AITD, autoimmune thyroid disease.

developed GO at 18 months. GO developed in 53 (15%) of the 348 patients, which was mild in 46 patients (13%) and moderate to severe in 7 patients (2%). Their characteristics at baseline and at time of GO diagnosis are shown in [Supplementary Table](#) (see section on [supplementary data](#) given at the end of this article). GO developed in 26 patients at 6 months (7.4%), in 18 patients at 12 months (5.1%), and in 9 patients at 18 months (2.5%) follow-up respectively. There was a direct relationship between the number of patients who developed GO and the number of patients recruited by each individual center ([Fig. 1](#)). Mixed model analysis also confirmed homogeneity between centers with respect to patient populations. Baseline characteristics of the 295 patients who did not develop GO and the 53 patients who developed GO are given in [Table 1](#). Patients who developed hyper GO tended to be older, had longer duration of hyperthyroid symptoms, were more often current smokers, consumed more cigarettes per day and had a higher number of pack-years. Serum TBII were also higher in patients who developed GO, but otherwise the biochemical severity of hyperthyroidism and choice for titration or block-and-replace regimen were similar in both groups. GO was further associated with a positive Vancouver Orbitopathy Rule and higher CAS scores at baseline. CAS >0 at baseline was observed in 36 patients: CAS of 1 was present in 34 patients and CAS of 2 in 2 patients. The distribution of the various

CAS items was as follows: mild eyelid swelling 10, plica/caruncle swelling 0, chemosis 0, spontaneous pain 4, pain on eye movement 3, mild redness of conjunctiva 7, redness of eyelids 14. One patient with CAS 2 had spontaneous pain and pain on movement, while the

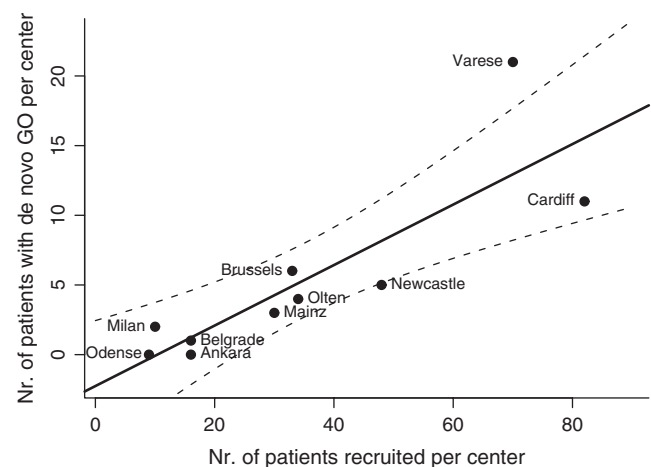


Figure 1

Direct relationship between number of patients recruited per center and number of patients developing Graves' orbitopathy (GO) per center ($r=0.85$, $P=0.002$) (AITD, autoimmune thyroid disease; AI, autoimmune; §, hyperthyroid symptoms until start of antithyroid drugs; †, mean ± s.d.; *, median values with interquartile range).

other with CAS 2 had mild eyelid swelling and mild redness of conjunctiva. Patients with scores 1 or 2 were collapsed in a single category (CAS > 0). GO developed in 12.5% of 312 patients with baseline CAS of 0, and in 39% of 36 patients with baseline CAS ≥ 1 ($P < 0.001$). Development of GO was thus associated with older age, current smoking, longer duration of hyperthyroid symptoms, higher TBII, higher CAS and a positive Vancouver Orbitopathy Rule.

Using mixed-effect logistic regression analysis, four variables were identified, which were independent of each other and predicted development or progression to obvious GO: CAS > 0, current smoking, TBII and duration of hyperthyroid symptoms; their odds ratios are listed in Table 2. In the multivariate analysis, age and the Vancouver Orbitopathy Rule were no longer independent determinants of GO. For each of the ten centers, probability of developing GO for the four variables is presented in Fig. 2.

A predictive score (Prediction of Graves' Orbitopathy (PREDIGO)) was constructed based on the four independent variables. Points were assigned to the presence or absence of each variable, and the sum of the points provides the numerical predictive score that ranges from 0 to 15 (Table 3). Scores > 6 have some predictive value for developing GO, whereas scores of ≤ 6 are not predictive of developing GO. Sensitivity of the predictive score is 0.56 (95% CI: 0.42–0.70), specificity 0.75 (0.70–0.79), positive predictive value 0.28 (0.20–0.37) and negative predictive value 0.91 (0.87–0.94). The area under the ROC curve of the predictive score is 0.71 (0.63–0.789) (Fig. 3). The proportion of patients who developed GO

among all patients with a particular predictive score is depicted in Fig. 4.

Discussion

Rate of GO development after the onset of Graves' hyperthyroidism

In this multicenter study, 15% of patients with newly diagnosed GH but without overt GO, developed GO

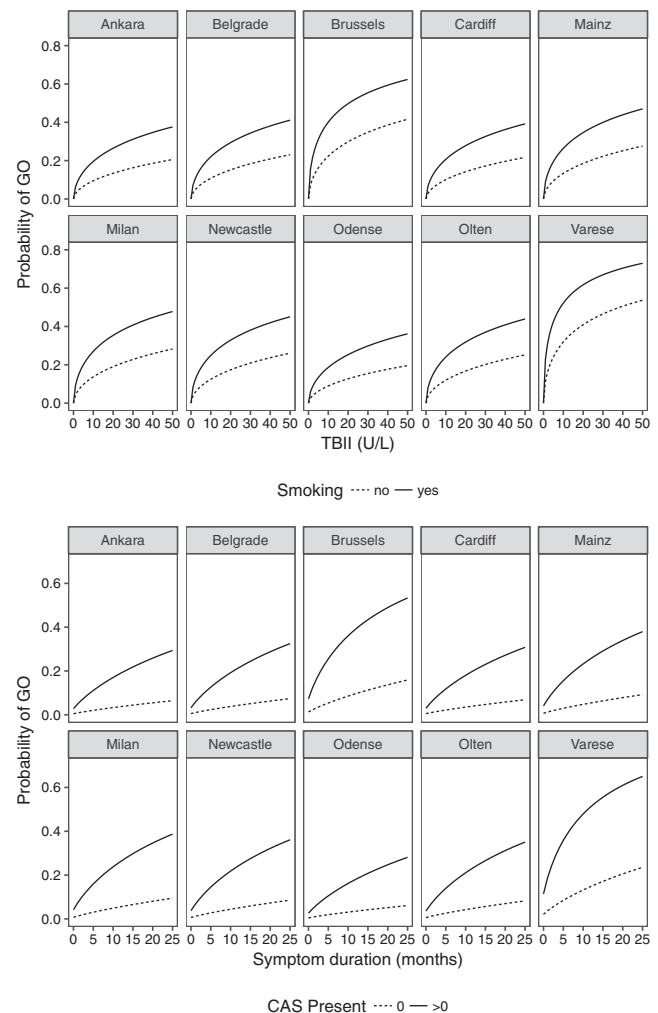


Figure 2

Probability of developing Graves' orbitopathy in patients with Graves' hyperthyroidism during 18-month treatment with antithyroid drugs per participating center, as a function of TBII and current smoking (top panels) and as a function of duration of hyperthyroid symptoms and clinical activity score (bottom panels).

Table 2 Baseline variables predicting development of GO in patients with Graves' hyperthyroidism treated for 18 months with antithyroid drugs.

Baseline variable predicting GO	Univariate odds ratio (95% CI)	P value
CAS 0	1.00	<0.01
CAS ≥ 1	4.45 (2.11–9.42)	
TBII < 2 (U/L)	1.00	
TBII 2–10 (U/L)	1.82 (0.93–3.54)	0.08
TBII > 10 (U/L)	3.75 (1.57–9.00)	<0.01
Duration hyperthyroid symptoms		
<1 month	1.00	
1–4 months	1.62 (0.82–3.19)	0.16
>4 months	3.35 (1.47–7.64)	<0.01
Current smoker no	1.00	<0.01
Current smoker yes	2.77 (1.53–5.05)	

Table 3 Predictive score for development of GO (PREDIGO) in patients with Graves' hyperthyroidism treated with antithyroid drugs for 18 months.

Baseline variable	Cut-off	Score
CAS	0	0
	≥1	5
TBII	<2 (U/L)	0
	2–10 (U/L)	2
	>10 (U/L)	5
Duration of hyperthyroid symptoms	<1 months	0
	1–4 months	1
	>4 months	3
Current smoking	No	0
	Yes	2

Maximum score 15.

during a follow-up of 18 months. The orbitopathy was mild in 13%, moderate to severe in 2% and occurred predominantly at 6–12 months after starting antithyroid drugs. Differences between centers did not seem to play a role for the frequency of GO, as the number of patients who developed GO was directly related to the number of patients recruited from that center (Fig. 1).

The data are remarkably similar to those of a recent single-center Italian study from Varese published in 2013 (3). In that study, 194 patients with GH but without overt GO were followed for 18 months during/after treatment with antithyroid drugs. GO developed in 12.9% (mild GO in 10.3%, moderate-to-severe GO in 2.6%), and most appeared 6–12 months after the start of treatment. At the time of diagnosis of hyperthyroidism, GO was absent in 74% and present in 26%. New GO following the diagnosis of GH occurred in 9.5% ($0.129 \times 74\%$), rendering a total GO frequency of 35.5% (26%+9.5%) in a population of GH. GO was diagnosed at the same time as GH in 73% (26 out of 35.5), whereas GO onset followed that of hyperthyroidism in 27% (9.5 out of 35.5). These figures are at variance with reports in the older literature, stating that GO develops after, simultaneously with or before GH in about 47, 38 and 15% respectively (20, 21, 22). The rates of GO cases developing after diagnosis of GH are apparently much higher in the past (47%) than at present (27%). Earlier diagnosis and treatment of hyperthyroidism, identification of the risks conferred by ¹³¹I therapy and post-radioiodine hypothyroidism and focus on the detrimental effects of smoking have likely contributed to this secular decline. The lower prevalence and incidence of late-onset GO seems to be the result of effective primary and secondary prevention of GO (23).

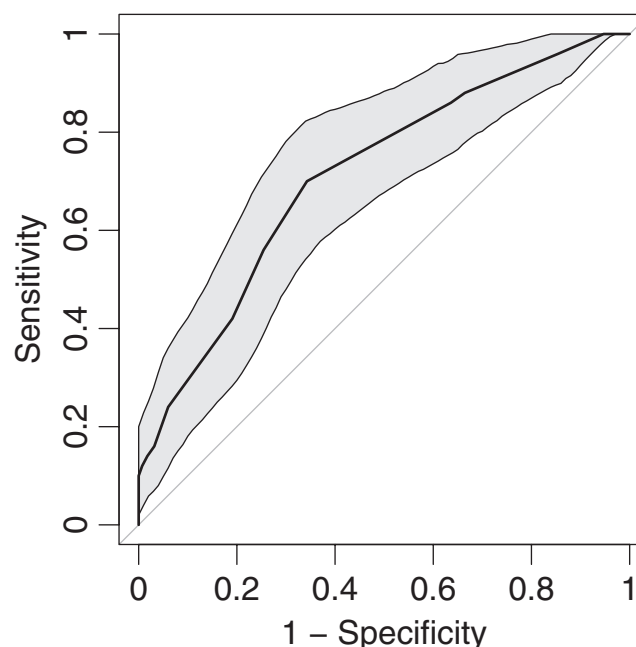


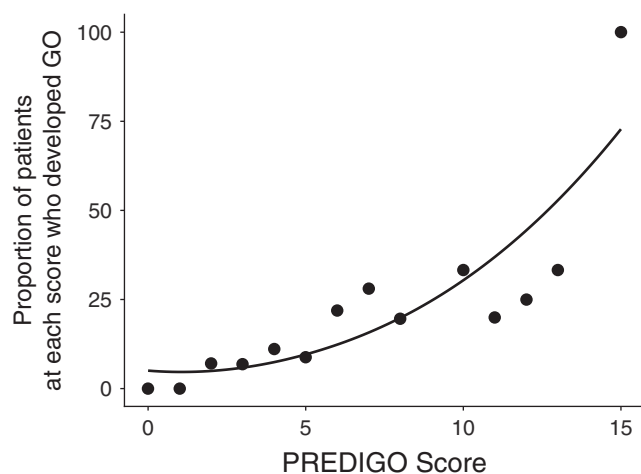
Figure 3

Receiver-operator curve with confidence intervals of the PREDIGO score for predicting development of Graves' orbitopathy in patients with Graves' hyperthyroidism treated for 18 months with antithyroid drugs.

Nowadays it is rare for a patient with GH who presents without GO to contract moderate-to-severe GO later in the course of the disease. Indeed, the clinical phenotype of Graves' disease is presently milder than that in the past (24, 25).

Determinants of GO development

We identified four independent determinants as predictors of GO development in patients with newly diagnosed GH: CAS, TBII, current smoking and longer duration of hyperthyroid symptoms. Associations between these items and GO are known from previous studies (8, 9, 10, 11, 12). However, this is the first time the association of these items with development of GO has been demonstrated in a prospective manner in hyperthyroid patients who had no overt GO at study entrance. It is not immediately clear why a longer duration of hyperthyroid symptoms is a predictor of GO. In a previous study among 251 consecutive patients with newly diagnosed GH, duration of symptoms >4 months was associated with younger age, higher TPOAb (thyroid peroxidase antibodies) levels, larger goiter size, but not with higher TBII (TSH-binding

**Figure 4**

Predictive score for development of Graves' orbitopathy in patients with Graves' hyperthyroidism treated with antithyroid drugs for 18 months, called the PREDIGO (PREDictor of Graves' Orbitopathy). Scores ≤ 6 are predictive of not developing GO, whereas scores > 6 have some predictive value for developing GO.

inhibitor immunoglobulins) or higher prevalence of GO (although the prevalence of GO was 19% at symptoms duration ≤ 4 months and increased to 28% at a duration ≥ 12 months, the trend was not significant) (26). One may hypothesize that longer duration of symptoms means longer exposure to TBII, which is associated with larger goiter size and by analogy may also lead to larger size of extraocular muscles and orbital fat.

Biochemically more severe GH has been associated with a higher risk of GO in a Swedish prospective randomized clinical trial (5). The slightly higher baseline serum FT4 in patients who developed GO in our study, although not statistically significant, points in the same direction.

Assessment of the extent of swelling and redness of the eyes remains subjective, and minor degrees may remain unnoticed and/or not necessarily indicate GO. We tried to increase objectivity in deciding whether eyelid swelling or conjunctival redness was absent or mild (allowing inclusion), or moderate to severe (patient excluded) with the help of a color atlas of eye changes in GO (15). Retrobulbar pain, mild eyelid swelling and/or mild conjunctival redness count in the CAS, which proved to be one of the main independent predictors of GO development. One may argue that these minor degrees of swelling, redness and pain already indicated the presence of GO at baseline. Even so, the PREDIGO

score retains its value in predicting progression of very mild (almost subclinical) GO to more overt GO. It is interesting that the Vancouver Orbitopathy Rule (asking among others also for redness in the eyes and redness or fullness of eyelids) had some predictive value in the univariate analysis, providing confirmation in an independent cohort of the association between a positive Vancouver Orbitopathy Rule and GO development (14). Its question 'Do your eyes seem to be wide open?' may reflect the slightly higher baseline values of lid aperture and proptosis in our patients who developed GO.

Other putative determinants of developing GO in our study could have been differences in the rate of control of hyperthyroidism and the extent to which euthyroidism was restored. Thyroid function tests were, however, not different between groups at 6, 12 and 18 months during treatment with antithyroid drugs (data not shown). There were no differences with respect to development of GO between patients who were treated with antithyroid drugs according the block-and-replace regimen or the titration regimen.

Quantitative predictive score for GO development

Based on the four independent determinants, we were able to construct a quantitative predictive score for the development of GO, called PREDIGO. The score ranges from 0 to a maximum of 15. Low scores are associated with a low probability of developing GO, and *vice versa*. PREDIGO had a high negative predictive value of 0.91 but a rather low positive predictive value of 0.28. In other words, it seems better at identifying those patients who escape GO than those who will develop GO. Improvement of the positive predictive value may have to await the development of more sensitive biomarkers for GO, which will likely depend on better insight into the pathogenesis of the disease. It remains to be demonstrated under which circumstances the score will be most useful in the management of Graves' disease patients. One may consider studies to evaluate whether a high predictive score would alter management, e.g. in refraining from ^{131}I therapy or starting with selenium. In case of a high predictive score, this could be used as a disease-specific argument to convince the patient to stop smoking.

Strengths and limitations

Strengths of our study relate to its prospective nature, its large sample size and the structured investigation according to a detailed protocol. Eye changes were

recorded predominantly by endocrinologists and not by ophthalmologists. Slit lamp investigations, which are performed exclusively by ophthalmologists, are thus not assessed in the present study. We view this as an advantage rather than a disadvantage. For newly diagnosed patients with GH without overt GO are nearly always managed by internists/endocrinologists. Thereby applicability of the results of this study for routine endocrine practice may be inferred.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-18-0039>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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