MANAGEMENT OF ENDOCRINE DISEASE

Predictive scores in autoimmune thyroid disease: are they useful?

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Abstract

Prediction models are of a great assistance for predicting the development of a disease, detecting or screening undiagnosed patients, predicting the effectiveness of a treatment and helping toward better decision-making. Recently, three predictive scores in the field of autoimmune thyroid disease (AITD) have been introduced: The Thyroid Hormones Event Amsterdam (THEA) score: a predictive score of the development of overt AITD, the Graves' Events After Therapy (GREAT) score: a prediction score for the risk of recurrence after antithyroid drugs withdrawal and the Prediction Graves' Orbitopathy (PREDIGO) score: a prediction score for the development of Graves' orbitopathy in newly diagnosed patients with Graves' hyperthyroidism. Their construction, clinical applicability, the possible preventative measurements which can be taken to diminish the risks and the potential future developments which can improve the accuracy of the predictive scores are discussed in this review.

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Introduction

The 21st century reserved a revolution for medicine: the transition from the 'one size fits all' approach to precision medicine, which is defined as an approach to treat and prevent a disease by taking into consideration the individual variability in genes, environment and lifestyle for each individual (1). Precision medicine aims to treat the right patient with the right drug at the right time. One cannot find a better example for its role other than treating cancer patients with the newly developed molecularly targeted therapies, which have resulted in better efficacy and lower toxicity. Precision medicine is expected to be

applied in all human diseases and autoimmune thyroid disease (AITD) cannot be an exception. AITD affects many people worldwide and encompasses a spectrum of conditions ranging from Hashimoto's hypothyroidism (HH) to Graves' hyperthyroidism (GH) (2).

Precision medicine is not limited only in treatment but contributes to the prediction, prevention, diagnosis and prognosis of diseases. Regarding prediction, it is important to identify the parameters which are associated with or can predict certain outcomes and to conduct clinical prediction models based on these parameters.

Invited Author's profile

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Prediction models can be of a great assistance for predicting the development of a disease, detecting or screening undiagnosed patients, predicting the effectiveness of a treatment and helping toward better decision-making (3). How can prediction models be applied in AITD? One example is the estimation of the risk for the development of overt AITD. It is well known that the risk for developing AITD is greater in members of families in which AITD occurs. But how great the risk is for a particular subject was, until recently, difficult to quantify. This has changed now with the development of the Thyroid Hormones Event Amsterdam (THEA) score which can calculate the risk for the development of overt AITD in women who are members of AITD families. And then the question from the subject with a given high calculated risk to develop overt AITD will arise: what can I do to prevent the disease?

In this review, I aim to describe three predictive scores in the field of AITD (the Thyroid Hormones Event Amsterdam (THEA) score: a predictive score of the development of overt AITD, the Graves' Events After Therapy (GREAT) score: a prediction score for the risk of recurrence after antithyroid drugs withdrawal and the Prediction Graves' Orbitopathy (PREDIGO) score: a prediction score for the development of Graves' Orbitopathy in newly diagnosed GH patients) and to discuss their clinical applicability, the possible preventative measurements taken to lower the risks and the potential future developments which can improve the accuracy and utility of the predictive scores.

Prediction of the development of AITD: the THEA score

Genetic contribution to the AITD pathogenesis was already observed in the 1940s. Early observational studies reported on the familial occurrence of AITD, revealing a family history of thyroid disease in up to 60% of GH patients (4, 5). Later, it was reported that one-third of the siblings of AITD patients developed AITD themselves (6) and Villanueva *et al.* estimated a high sibling recurrence risk ratio (λ_s) for AITD (11.6 for GH and 28.0 for HH) (7). Stronger evidence for the AITD genetic predisposition comes from twin studies, which suggest that the concordance rate for GH and HH is significantly higher in monozygotic twins compared with dizygotic twins (0.35 vs 0.03, $P=0.001$ and 0.55 vs 0.0, $P=0.01$ for GH and HH respectively) (8, 9). A model fitting analysis estimated that 79 and 73% of the likelihood of developing GH and thyroid antibodies respectively is due to genetic factors (10, 11, 12), and it can be assumed that the relative impact

of genetic factors in the phenotypes of AITD is most likely around 75% (11).

Until recently it was difficult to quantify the risk for the development of overt AITD in a member of an AITD family. A large observational prospective study was conducted in Amsterdam in order to make a predictive score for the development of overt autoimmune hypo- or hyperthyroidism (13). The study cohort, named the Amsterdam AITD cohort, consisted of 790 euthyroid healthy female subjects who had at least one first- or second-degree relative with documented autoimmune hyperthyroidism or hypothyroidism. All subjects were 18–65 years old without a history of thyroid disease. Endpoints of follow-up were the development of overt hyperthyroidism or hypothyroidism (called events) defined by abnormal thyroid-stimulating hormone (TSH) values in combination with abnormal fT4 concentrations in plasma. Endpoints were assessed every year for 5 years. At each visit, blood was sampled for TSH, fT4 (free thyroxine), TPOAb (antithyroid peroxidase antibodies), TgAb (anti-thyroglobulin antibodies) and TBII (TSH-binding inhibitory immunoglobulins). In addition, annual questionnaires assessed smoking habits, alcohol consumption, use of oral contraceptives or other estrogens, pregnancies and stress exposure.

At the end of the 5-year follow-up, 38 subjects had developed autoimmune hypothyroidism (34 HH and 4 postpartum thyroiditis) and 13 autoimmune hyperthyroidism (11 GH, 1 postpartum thyroiditis and 1 silent thyroiditis). Multiple logistic regression analysis identified serum TSH level, TPOAb concentration and family background as independent risk factors for the development of overt AITD. An abnormal TSH at study entrance clearly constituted a risk, but the risk started to increase already at TSH levels above 2.0 mIU/L. A level-dependent effect was also observed for TPOAb concentration. Having two relatives with HH enhances the risk. Age was not an independent risk factor; nor was TgAb presence or concentration. None of the putative environmental factors affected hazard ratios significantly. A simplified model was obtained by the logistic regression model by putting weights to individual risk factors proportional to their relative risks. This model allowed the calculation of a predictive score called the Thyroid Events Amsterdam (THEA) score (Table 1).

The findings from the Amsterdam AITD cohort are in agreement with other studies. The incidence rates reported in the prospective British Wickham study were 3.5 and 0.80 per 1000 women per year for hypothyroidism and hyperthyroidism respectively (14). The incidence rates in

Review	G Effraimidis	Predictive scores in AITD	181:3	R121
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Table 1 Calculation and risk stratification of the Thyroid Hormones Event Amsterdam (THEA) score.

	RR (%)	Hypothyroid event	Hyperthyroid event	Any event
Risk stratification of THEA				
Low: 0–7	2.6			
Medium: 8–10	13.1			
High: 11–15	32.9			
Very high: 16–21	59.4			
Calculation of scores				
TSH, mU/L				
<0.4		0	2	2
0.4–2.0		0	0	0
2.1–4.0		3	–1	2
4.1–5.7		6	–2	4
>5.7		9	–3	6
TPO antibodies, kU/L				
<100		0	0	0
100–1000		3	1	4
1001–10,000		6	2	8
>10,000		9	3	12
Family background				
2 relatives with Graves'		0	1	1
2 relatives with Hashimoto		3	0	3
Maximum score		21	6	21

RR, relative risk; TPO, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

the Amsterdam AITD cohort lie between the lower risk in the British general population (2.7 and 4.1 times higher for hypo- and hyperthyroidism respectively compared with the British general population) and the higher risk in siblings (sibling recurrence risk ratio (λ_s) 28.0 for HH 11.6 for GH (7)). TSH was an independent risk factor for the development of hypothyroidism in the Wickham survey (14), in a longitudinal community-based study from Australia (15) and in the Norwegian HUNT study (16). In line with the Amsterdam AITD cohort, the first two studies reported that the risk of developing hypothyroidism sharply increased at TSH above 2.0–2.5 mIU/L independent of the TPOAb status (14, 15). Progressively increasing risk with increasing TPOAb concentration, independent of TSH levels, has been observed in the Wickham survey (14). On the contrary, the Wickham survey failed to find an association of increased odds of developing hypothyroidism with a positive family history. This is so, because this study evaluated the general population and not AITD family members exclusively.

With the help of the THEA score, physicians are now able to answer with great precision the frequently asked question by patients with AITD 'will my daughter also get the disease?'. Lower THEA means lower risk on developing overt AITD in the following 5 years (Table 1). Consequently, a woman from an AITD families with a low THEA scores (0–7) can be reassured that she will most likely maintain a normal thyroid function in the next

5 years. On the contrary, a woman with high THEA scores can be advised to be reassessed in shorter intervals. The THEA score is of high importance for women who plan a pregnancy in the next few years taking into consideration the possible adverse pregnancy outcomes with abnormal thyroid function and thyroid autoimmunity (17).

Can the THEA score be applied to male AITD relatives? This is yet not known. One can speculate that the THEA score could be applicable to male AITD relatives and this in view of the higher odds for developing hypothyroidism in males than in females reported in the Wickham study (14). Raised TSH alone, higher TPOAb concentration alone and both raised TSH and higher TPOAb concentration had higher odds ratios. Therefore, one could support that at a given THEA score the risk will be greater in male than in female AITD relatives.

None of the factors involved in THEA score (TSH, TPOAb, family background) are modifiable (Table 2). Moreover, none of the baseline environmental determinants in the Amsterdam AITD cohort significantly affected hazard ratios for the development of overt AITD, although it is known that some of them constitute a risk for both GH and HH, while others are risk factors just for one of the AITDs and protective for the other. Current smoking is risk factor for the development of GH (18) but protective for the development of HH (19, 20, 21) and thyroid antibodies (22). Moderate alcohol consumption has been found to be protective for both GH (23, 24)

Review	G Effraimidis	Predictive scores in AITD	181:3	R122
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Table 2 Predictive scores in AITD. Utility, applicable populations, modifiable and non-modifiable predictor factors and determinants.

	THEA score	GREAT score	PREDIGO score
Utility population	Estimation of the risk of the development of overt AITD in females with first- or second-degree relatives of AITD patients	Estimation of the risk of recurrence of GH after ATDs discontinuation in newly diagnosed GH patients	Estimation of the risk of the development of GO in newly diagnosed GH patients without overt GO undergoing ATDs treatment
Predictive factors involved in the score			
TSH levels	Non-modifiable		
TPOAb levels	Non-modifiable		
Family history	Non-modifiable		
ft4 levels		Non-modifiable	
Age		Non-modifiable	
TBII levels		Non-modifiable	Non-modifiable
Goiter size		Non-modifiable	
Duration of hyperthyroid symptoms			Non-modifiable
Genetic polymorphisms		Non-modifiable	
CAS score			Non-modifiable
Smoking			Modifiable. Increases risk of the development of GO
Determinants NOT involved in the score			
Smoking	Modifiable. Decreases risk of HH. Increases risk of GH	Modifiable. Possible risk factor for recurrence	
Gender		Non-modifiable. Maybe recurrence rate males > females	Non-modifiable. Maybe the risk for the development of GO males > females
Age			Non-modifiable. Older age is a risk factor for the development of GO
Moderate alcohol intake	Modifiable. Decreases risk of both HH and GH		
Pregnancy	Modifiable. Increases risk of both HH and GH		
Presence of Graves' orbitopathy		Non-modifiable. Maybe risk factor for recurrence	
Biochemical severity of GH			Non-modifiable. Higher probability of GO with higher baseline T3
Stress	Modifiable? Doesn't change risk of HH. Increases risk of GH		
Selenium	Modifiable. Unknown effect, data still inconclusive		
Vitamin D	Modifiable. Unknown effect, data still inconclusive		

Utility, applicable populations, modifiable and non-modifiable predictor factors and determinants.

AITD, autoimmune thyroid disease; ATDs, antithyroid drugs; CAS, clinical activity score; EUGOGO, European Group on Graves' Orbitopathy; ft4, free thyroxine; GH, Graves' hyperthyroidism; GO, Graves' orbitopathy; GREAT, Graves' Events After Therapy; PREDIGO, Prediction Graves' Orbitopathy; TBII, TSH-binding inhibitory immunoglobulins; THEA, Thyroid Hormones Event Amsterdam; TPOAb, antithyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

and HH (25), but not for TPOAb (24). The proportion of pregnant women and women in the postpartum period was higher in those developing overt AITD than those remaining euthyroid in the Amsterdam AITD cohort (26). Stress is a provocative factor for GH (27), while stressful life events and daily hassles demonstrated no association between stress exposure and *de novo* occurrence of TPOAb or autoimmune hypothyroidism (28).

Based on the above, it can be concluded that currently no preventative strategy could be followed in order to diminish the risk of a subject with AITD relatives (2). Discontinuation of smoking would shift the risk from GH to HH. Refraining from planning a pregnancy or avoiding stress does not constitute reasonable advice. Moderate alcohol consumption would make sense. Lately, the relationship between vitamin D (29, 30) or selenium and

Review	G Effraimidis	Predictive scores in AITD	181:3	R123
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AITD (31, 32) has drawn much attention but data are still inconclusive with the exception of the role of selenium supplementation in mild Graves' orbitopathy (GO) and in the postpartum period. Selenium supplementation has been proven to prevent deterioration of mild GO in European countries with mild selenium deficiency (33). If selenium supplementation is equally effective in selenium-sufficient countries, for example the USA, is still unknown. The impact of selenium supplementation in postpartum thyroiditis was evaluated by one randomized control trial which demonstrated a reduction in postpartum thyroiditis with selenium administration (34). These results are yet to be confirmed by more studies before supporting routine selenium supplementation in TPOAb-positive pregnant women.

The THEA score has not been validated externally thus far. It can be argued that the relatively low number of events probably makes the THEA score less accurate. Therefore, the authors evaluated the THEA score in the Amsterdam AITD cohort comparing the observed with the expected event rates (13). They found a good agreement between both observed and expected event rates and, therefore, they concluded for the strong operational value of the THEA score. Nevertheless, there is still a need to validate the THEA score in other populations.

Prediction of the risk of recurrence after antithyroid drugs withdrawal: the GREAT score

The current available treatment options for GH are either medical treatment with antithyroid drugs (ATDs) or ablative treatments (35). Three ATDs are commercially available including methimazole (MMI), propylthiouracil and carbimazole. Ablative therapies include radioactive iodine treatment (RAI) or the surgical removal of the thyroid tissue. All available treatment options are effective and relatively safe and the initial therapeutic strategy for a newly diagnosed patient with GH remains a choice that the patient and the treating physician could take together after discussing each of the treatment options, including among others the drawbacks and the potential side effects (36, 37).

Already since the early 1940s, after the very first use of ATDs in hyperthyroid patients, it has been observed that hyperthyroidism recurred when the ATDs were discontinued. It should be mentioned that the terms 'relapse' and 'recurrence' are being used when hyperthyroidism returns within 3 months or in more

than 3 months of the ATDs discontinuation respectively (38). In this review the term recurrence will be used to describe the development of GH after ATDs withdrawal at any time point. The recurrence rate has been estimated to be about 50%, with a high variation between 30 and 70% (39, 40, 41, 42). Consequently, the recurrence of GH after ATDs discontinuation remains the main drawback of the medical treatment resulting in potential disappointment for the patient (43). On the contrary, ablative treatments eliminate any risk of recurrence but at the expense of the development of permanent hypothyroidism.

The identification of the factors that could predict the recurrence of GH after ATDs discontinuation is a necessity in order to make the best management decision in patients with a first episode of GH. Parameters such as age, biochemical disease severity, TRAb (TSH receptor antibodies) or TBII levels, goiter size and smoking have been identified as putative determinants. However, most of these studies evaluated these determinants at the time of the ATDs' withdrawal and not the time of diagnosis. A recent meta-analysis assessed the potential pretreatment risk factors of relapse of GH including 54 studies published since 1977 (44). This meta-analysis reported a relapse rate of 48.7% among 7595 patients and found that the occurrence of orbitopathy, smoking, larger thyroid volume and biochemical severe disease (fT4, TT3, TRAb, TBII and TSAb levels) were associated with a higher risk of recurrence. Nevertheless, these markers, alone or combined, were not strong enough to predict the clinical outcome of a single patient.

Recently, a group from the Netherlands developed two predictive scoring systems for GH recurrence (45). The first, named the Graves' Recurrent Events After Therapy (GREAT) score, is based on clinical and biochemical variables before the initiation of the ATDs. The second, named GREAT+ score, is an enhanced predictive score which combines genetic markers in addition to the clinical and biochemical parameters used in the GREAT score. In this Dutch study, 178 newly diagnosed GH patients received block and replacement regimen for 1 year, consisting of 30mg MMI and levothyroxine in a dose to maintain normal fT4. Patients were followed for 2 years after the treatment's discontinuation. Thirty-seven percent of the participants had a recurrence within 2 years after withdrawal of the ATDs in agreement with the reported recurrence rates in the literature. Identified risk factors for recurrence were higher serum fT4, younger age, higher TBII and larger goiters. Sex, smoking, orbitopathy, pretibial myxedema and TPOAb were not independent risk factors for recurrence. Regarding the genetic

polymorphisms, *PTPN22* SNP and human leukocyte antigen (*HLA*) polymorphisms *DRB1-03*, *DQA1-05* and *DQB1-02* were found to be predictors for recurrence, while *CTLA4-49* and *CTLA4-60* SNPs were not associated with higher recurrence.

Based on a multivariate model, a six-point GREAT and a ten-point GREAT+ scoring system were developed (Table 3). Calculation of the score(s) is as follows: age (<40 and ≥40 years: 1 or 0 point), serum fT4 (<40 and ≥40 pmol/L: 0 or 1 point), serum TBII (<6; 6–19.9; >19.9 IU/L: 0, 1 or 2 points), WHO grades for goiter (grade 0–I, II–III: 0 or 2 points), number of *HLA* polymorphisms

(0; 1–2; 3: 0, 2 or 3 points), carriage of *PTPN22* C/T polymorphism (1 point). The scores were stratified into classes according to recurrence risk (Table 3): class I (GREAT score 0–1, GREAT+ score 0–2), class II (GREAT score 2–3, GREAT+ score 3–4), class III (GREAT score 4–6, GREAT+ score 5–6) and class IV (GREAT+ score 7–10).

Some studies have found a higher recurrence rate in males than in females (39, 42, 46), but this was not confirmed by the meta-analysis of Struja *et al.* (44), where sex did not show to have a significant impact (Table 2). Young age has been identified as a risk factor in the GREAT score and in a large number of studies (39, 42, 47, 48) but not in the meta-analysis (44). Smoking has been observed as a risk factor in some studies, the meta-analysis included (44, 49, 50) but was not an independent risk factor in the Dutch study (45). There is consensus regarding the goiter size and the biochemical severity of the GH as risk factors for recurrence (39, 41, 44, 45, 47). Levels of TRAb/TBII were shown to have high predictive value (44, 45). GO has been reported as one of the clinical risk factors of recurrence of GH (44, 51) but not all studies agree on this finding (45, 52, 53). In a retrospective study in children, it has been found that goiter size, younger age, not Caucasians, TRAb levels and fT4 levels are associated with a higher recurrence rate (54), while prospective studies in children reporting younger age and high thyroid levels as risk factors for recurrence (55, 56).

The higher concordance rate of GH in monozygotic than in dizygotic twins is clearly an indicator of the genetic influence on the pathogenesis of GH (10). Immune-regulatory genes, including *HLA*, *CD40*, cytotoxic T-lymphocyte-associated factor 4 (*CTLA4*), protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) and Fc receptor-like protein 3 (*FCRL3*), have been observed as genetic determinants of GH (2). In addition, thyroid autoantigen genes are also associated with GH (57). However, GD genetic predisposition is not yet fully elucidated and studies carried out in different ethnic populations with different research methodologies have reported conflicting results regarding the genetic predictors for the recurrence of GH.

The GREAT score (Table 3) is based on easily collected clinical parameters at the time of GD diagnosis and, therefore, it is easily applicable in the everyday clinical practice. It seems reasonable to support that a recurrence risk of around 25% favors the medical treatment and a recurrence risk of 75% favors thyroid ablation. A recurrence rate of approximately 50% is inconclusive and all available treatments are open to discussion. Therefore, for patients falling into the low recurrence risk class I, ATDs would be

Table 3 Calculation and risk stratification of the Graves' Events After Therapy (GREAT) score.

Marker	RR (%)	GREAT score	GREAT+ score
Risk stratification			
GREAT			
Class I: 0–1	16		
Class II: 2–3	44		
Class III 4–6	68		
GREAT+			
Class I: 0–2	4		
Class II: 3–4	21		
Class III: 5–6	49		
Class IV: 7–10	84		
Calculation of scores			
Age (years)			
≥40		0	0
<40		1	1
Serum fT4 (pmol/L)			
<40		0	0
≥40		1	1
Serum TBII (IU/L)			
<6		0	0
6–19.9		1	1
≥20		2	2
Goiter size (WHO)			
0–I		0	0
II–III		2	2
<i>HLA</i> polymorphisms (number)*			
0			0
1–2			2
3 (LD)			3
<i>PTPN22</i>			
Wild type			0
C/T			1
Maximum score		6	10

Goiter size grade 0, thyroid not or distinctly palpable but usually not visible with head in a normal or raised position; grade I, thyroid easily palpable and visible with the head in either a normal or raised position; grade II, thyroid easily visible with the head in a normal position; grade III, goiter visible at a distance.

**HLA* subtypes *DQB1-02*, *DQA1-05* and *DRB1-03*.

HLA, human leukocyte antigen; LD, linkage disequilibrium; *PTPN22*, protein tyrosine phosphatase, non-receptor type 22; RR, relative risk; T4, free thyroxine; TBII, TSH-binding inhibitory immunoglobulins.

the preferable initial treatment. For patients falling into the high recurrence risk class III, the consideration of an ablative treatment would be more reasonable. For patients falling into the intermediate recurrence risk class II, it will be necessary to calculate the GREAT+ score by the adjuvant measurement of *HLA* polymorphisms and *PTPN22* SNP. Patients in the class I+ and II+ of the GREAT+ score may start ATDs while those in the class IV+ of the GREAT+ score may be offered an ablative treatment. The rest (class III+ of the GREAT+ score) can be treated according to the preferences of the patient or the physician and existing comorbidities (Fig. 1).

The GREAT, but not the GREAT+, score has been externally validated by a Swiss (58) and an Italian (59) retrospective analysis of 741 and 387 patients respectively.

Figure 1

Application of the GREAT and GREAT+ in newly diagnosed GH patients. For GREAT class I patients (low recurrence risk), ATDs would be the preferable initial treatment. For GREAT class III patients (high recurrence risk), the consideration of an ablative treatment would be more reasonable. Adding genetic markers for GREAT class I and GREAT class III patients will not change the treatment approach. Genotyping for the GREAT class II patients (intermediate recurrence risk) will be necessary. Patients in the GREAT+ class I and GREAT+ II may start ATDs. Patients in the GREAT+ class IV may be offered an ablative treatment. The rest (class III+ of the GREAT+ score) can be treated according to the preferences of the patient or the physician and existing comorbidities. ATDs, antithyroid drugs; ft4, free thyroxine; GH, Graves' hyperthyroidism; GREAT, Graves' Events After Therapy; RAI, radioactive iodine; RR, relative risk; TBII, TSH-binding inhibitory immunoglobulins.

Both studies, despite their similarities and differences with the Dutch study, show a comparable prediction power especially for the GREAT class II and III patients. The risk of relapse in class I was higher in the two external studies (33.8% in the Swiss and 33.6% in the Italian study vs 16% in the Dutch study). This discrepancy is unexplained and in no case does it affect the proposed treatment plan for GREAT class I patients but the strength of the prospective design of the Dutch study should be underscored.

Prediction of the development of GO: the PREDIGO score

GO is the most common extrathyroidal manifestation of GH. It has been reported that up to 50% of the GH patients develop GO to some degree (60, 61). However, the GO prevalence has shown a considerable decline in the last decades (62). GO is associated with GH in around 90% of the cases (63), while the rest 10% is associated with other autoimmune thyroid disorders. GO has an unpredictable natural history and, therefore, it runs the risk of late diagnosis and delayed treatment. In this respect, the identification of potential determinants which could estimate the risk of GO development in newly GH diagnosed patients would be of great help.

The European Group on Graves' Orbitopathy (EUGOGO) conducted a multicenter prospective cohort study in 348 newly diagnosed untreated GH patients without overt GO in order to construct a predictive score for developing GO during an 18-month ATDs treatment course (64). The determinants assessed at baseline and before the ATDs initiation were age, sex, family history of AITD, other autoimmune diseases, duration of hyperthyroid symptoms, biochemical and immunologic severity of hyperthyroidism (TSH, ft4, ft3, TBII, TPOAb), smoking status (never smoker, exsmoker, current smoker), clinical activity score (CAS) and the Vancouver Orbitopathy Rule (65). Follow-up visits at 6, 12 and 18 months included blood sampling and reassessment of smoking behavior and eye changes. End points were the development of GO or the discontinuation of ATDs after 18 months of treatment.

GO occurred in 15% of the patients, 87% of those developed mild and 13% moderate-to-severe GO and it developed mainly 6–12 months after initiation of the ATDs treatment. These numbers are in agreement with an Italian study in which GO developed in 12.9% of the 194 newly diagnosed GH patients (10.3% mild, 2.6% moderate-to-severe GO) in a 6- to 12-month duration (66).

Patients who developed GO tended to be older (45.7 vs 42.4 years, $P=0.087$), had longer duration of hyperthyroid symptoms ($P=0.007$), were more often current smokers ($P=0.002$) and heavier smokers ($P=0.022$), had higher serum TBII (11.0 vs 6.4 U/L; $P=0.006$), had more often positive Vancouver Orbitopathy Rule ($P=0.075$) and higher CAS scores at baseline ($P<0.001$). Biochemical severity of hyperthyroidism and choice for titration or block-and-replace regimen were similar in both groups. Logistic regression and multivariate analysis identified four variables that were independent of each other and predicted development or progression to GO: a CAS >0 (Odds ratio, OR=4.45 for CAS ≥ 1), current smoking (OR=2.72), higher TBII level (OR=3.75 for TBII level >10 U/L) and duration of hyperthyroid symptoms (OR=3.35 for duration >4 months).

From the independent variables, a 15-point predictive score of GO, named Prediction of Graves' Orbitopathy (PREDIGO), was constructed (Table 4). Scores >6 have some predictive value for developing GO, while scores ≤ 6 were predictive of no GO. The PREDIGO had a high negative predictive value (0.91) but a low positive predictive value (0.37) and therefore it is more helpful in identifying the patients where GO is unlikely rather than those where GO is likely to develop.

Several studies have found that older age is a risk factor for the development of GO in GH patients (67, 68, 69). In a population-based study from Denmark, the incidence rate for GO was higher in 40–60-year-old GH patients compared to the less than 40-year-old GH patients (~ 8 vs $<2\%$ respectively). Regarding gender, a large longitudinal cohort (70) and a population study (71) did not show

any difference in the risk for developing GO in males and females, in contrast with other studies that have found a gender influence (67, 69).

The only so far biochemical predictive marker for the occurrence of GO is TRAb. TRAb levels were shown to have prognostic value for the occurrence of GO in GH patients and correlate with the activity and severity of TAO (72, 73, 74, 75). Moreover, high TRAb levels offer a definite risk of exacerbation or *de novo* development of GO in GH patients receiving RAI treatment (76, 77). In newly diagnosed GH patients, the probability of developing or exacerbation of GO was greater with higher baseline T3 concentrations (76), but in an observational prospective study, the biochemical severity of GH at presentation did not influence the development of GO (66). However, restoration and maintenance of euthyroidism is highly recommended in GH patients (78) as dysthyroidism has been associated with GO worsening (79). In addition, hypothyroidism following ablative treatments leads to deterioration of GO (80, 81). It has been supported the ATDs have no influence on the course of GO (82, 83). However, a recent prospective case-control study identified that usage of ATDs was negatively correlated with GO (68) and a recent large longitudinal cohort study found that thyroidectomy significantly reduces the hazard for GO (71). If this is confirmed by prospective studies, then thyroidectomy might become the treatment of choice in GH patients with high risk to develop GO, which underlines the necessity of the development of an accurate predictive score for the development of GO in GH patients.

The role of genetic factors in GO has not yet been clarified and therefore no genetic factor has been so far linked with the prediction of GO in GH patients (84, 85). A recent genome-wide association analysis compared GO patients to GH patients without GO found that a common genetic variant in *MACROD2* may increase susceptibility for GO (86). Whether this variant can contribute to the GO prediction is to be investigated.

With the exception of smoking, none other of the predictive factors in the PREDIGO score is modifiable (TBII level, CAS and duration of hyperthyroid symptoms) (Table 2). Refraining from smoking falls into the primary, secondary and tertiary prevention of GO and therefore the importance of smoking discontinuation should be underlined to all patients with GH, irrespectively of their estimated risk for the development of GO with the PREDIGO score (78).

The PREDIGO score offers a better insight into the predictive factors for GO in newly diagnosed patients

Table 4 Calculation of the Prediction Graves' Orbitopathy (PREDIGO) score.

Determinant	PREDIGO
CAS	
0	0
≥ 1	5
Serum TBII (IU/L)	
<2	0
2–10	2
>10	5
Duration of hyperthyroid symptoms (months)	
<1	0
1–4	1
>4	3
Current smoking	
No	0
Yes	2
Maximum score	15

CAS, clinical activity score; TBII, TSH-binding inhibitory immunoglobulins.

initially free from overt GO. Its high negative predictive value (0.91) allows the identification of low-risk patients and physicians can appease low-risk patients that the likelihood of the occurrence of GO is minimal. This can be of great importance in the modern era of internet self-diagnosis, where patients often encounter conflicting information on the internet, as mostly the worst possible scenarios and pictures with patients with severe GO are presented online. Moreover, the PREDIGO score could be a useful tool in the design of future studies on the prevention of GO. Currently, the stronger negative than positive protective value would not impact the treatment plan.

Future perspectives

The developments of precision medicine in AITD with the increasing numbers of -omics (i.e. genomics, proteomics, metabolomics etc.) are expected to provide new markers which will contribute to the enhancement of the predictive scores. In addition, the determination of a more precise genetic and molecular profile of an individual might enhance the accuracy of the predictive scores in AITD (Table 5).

TSH and fT4 serum concentrations are risk factors involved with the described predictive scores described above. An individual variability in the TSH and thyroid hormones concentrations has been reported (87, 88) but, so far, it is not feasible to determine the specific reference range for any given individual. This might be resolved in the future with the determination of the genetic profile of an individual as the thyroid hormone individual variability is likely to be due to genetic factors (89). Moreover, although the performance of the current TRAb assays is almost excellent, still about 5% of GD patients have undetectable TRAb (72). In addition, patients with

autoimmune hypothyroidism might have detectable TRAb which are actually blocking TRAb. Consequently, the development of more sensitive TRAb assays could solve these problems and improve the accuracy of the predictive scores.

Susceptibility genes for AITD can be divided to the genetic polymorphisms of immune-related genes (major histocompatibility complex class II molecules, cytotoxic T-lymphocyte antigen 4, protein tyrosine phosphatase, non-receptor type 22) and genes related to thyroid antigens (the TSH receptor and thyroglobulin). The available data strongly suggests that there must be many more still undetected susceptibility genes contributing to the development of AITD, but also genes which may confer protection for the development of AITD. The assessment of the known genes so far, but also of the possible gene polymorphisms identified in the future might be useful for prognostic purposes and might enhance the predictability of the AITD scores. An individual's genetic and molecular profile might also help with the modification of ATDs' doses or predict the development of potentially life-threatening side effects (i.e. agranulocytosis and hepatotoxicity). An area that might also be helpful is gene-environment interactions. Studies in this area have scarcely been conducted in thyroid autoimmunity. An exception is a Brazilian study on genetic polymorphisms associated with cigarette smoking and the risk of Graves' disease (90).

Markers that predict the risk for the development of AITD at very early stages, that is abnormalities in immune-competent cells in the early stage of thyroid autoimmunity before TPOAb become detectable in serum might be helpful in the prediction of the development of AITD. Studies conducted in the Amsterdam AITD cohort, found that euthyroid females' AITD relatives have a characteristic pattern of abnormalities in serum levels of growth factors, chemokines, adhesion molecules and cytokines (91, 92). The relatives who seroconverted to TPOAb differ from those who did not seroconvert by an upregulation of pro-inflammatory compounds. These compounds or other potential immunomarkers occurring in the very early stages of AITD might serve as predictive markers for the development of AITD and enhance the predictive scores in thyroid autoimmunity. Additionally, the identification of a specific biochemical marker of GO will be very helpful for the prediction of the development of GO.

The influence of the gut microbiota over non-intestinal autoimmune diseases has been receiving growing attention in recent years (93). It has been

Table 5 Possible future developments in the prediction of AITD.

Individualization of TSH and thyroid hormones reference ranges
Development of more sensitive TRAb assays
Genotyping more susceptibility genes for AITD (protective genes?)
Genotyping susceptibility genes for GO
Evaluation of the gene-environment interactions
Identification of immune markers in the very early stages of AITD, before the occurrence of TPOAb
Identification of specific biochemical marker for GO
Elucidation of the influence of the gut microbiota and intestinal dysbiosis on AITD

AITD, autoimmune thyroid disease; GO, Graves' orbitopathy; TPOAb, antithyroid peroxidase antibodies; TRAb, TSH receptor antibodies; TSH, thyroid-stimulating hormone.

suggested that changes of the intestinal microbiota could affect the balance of T-regulatory cells and T-helper 17 cells at the intestine, modifying the immune response of non-intestinal autoimmune diseases. Studies reported that subjects on the way for the development of clinical type 1 diabetes are characterized by intestinal dysbiosis, defined as imbalanced gut microbial ecosystem (94). Maybe this also applies for AITD and intestinal dysbiosis might be a predictive factor for AITD. This is yet to be proven, as currently very little is known about the impact of microbiota in AITD (95).

Autoimmune diseases are among the leading causes of death among young- and middle-aged women (96) and the development of interventions resulting in the delay, pause or reversal of autoimmune diseases will be revolutionary. Efforts are being made toward that direction. Nevertheless, there is still a long way to go until the development of approaches inducing antigen-specific tolerance. This is also true for the AITD (97) which although it is easily diagnosed and fully treatable, with the exception of GO, it still has a significant impact not only on the medical care utilization and cost but, most importantly, on the patients' quality of life. The application of these approaches require accurate prediction of individuals at risk with accurate and easily applicable prediction models.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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References

- Genetics Home Reference. Precision medicine, Published March 19, 2019. Bethesda, MD, USA: Lister Hill National Center for Biomedical Communications, U.S. National Library of Medicine, National Institutes of Health, Department of Health & Human Services, 2019. (available at: <https://ghr.nlm.nih.gov/primer/precisionmedicine/definition>)
- Effraimidis G & Wiersinga WM. Mechanisms in endocrinology: autoimmune thyroid disease: old and new players. *European Journal of Endocrinology* 2014 **170** R241–R252. (<https://doi.org/10.1530/EJE-14-0047>)
- Lee YH, Bang H & Kim DJ. How to establish clinical prediction models. *Endocrinology and Metabolism* 2016 **31** 38–44. (<https://doi.org/10.3803/EnM.2016.31.1.38>)
- Barrels ED. *Twin Examinations: Heredity in Graves' Disease*, pp 32–36. Copenhagen, Denmark: Munksgaard, 1941.
- Martin L. The hereditary and familial aspects of exophthalmic goitre and nodular goitre. *Quarterly Journal of Medicine* 1945 **14** 207–219.
- Hall R & Stanbury JB. Familial studies of autoimmune thyroiditis. *Clinical and Experimental Immunology* 1967 **2** (Supplement) S719–S725.
- Villanueva R, Greenberg DA, Davies TF & Tomer Y. Sibling recurrence risk in autoimmune thyroid disease. *Thyroid* 2003 **13** 761–764. (<https://doi.org/10.1089/105072503768499653>)
- Brix TH, Kyvik KO & Hegedus L. A population-based study of chronic autoimmune hypothyroidism in Danish twins. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 536–539. (<https://doi.org/10.1210/jcem.85.2.6385>)
- Brix TH, Christensen K, Holm NV, Harvald B & Hegedus L. A population-based study of Graves' disease in Danish twins. *Clinical Endocrinology* 1998 **48** 397–400. (<https://doi.org/10.1046/j.1365-2265.1998.00450.x>)
- Brix TH, Kyvik KO, Christensen K & Hegedus L. Evidence for a major role of heredity in Graves' disease: a population-based study of two Danish twin cohorts. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 930–934. (<https://doi.org/10.1210/jcem.86.2.7242>)
- Brix TH & Hegedus L. Twin studies as a model for exploring the aetiology of autoimmune thyroid disease. *Clinical Endocrinology* 2012 **76** 457–464. (<https://doi.org/10.1111/j.1365-2265.2011.04318.x>)
- Hansen PS, Brix TH, Iachine I, Kyvik KO & Hegedus L. The relative importance of genetic and environmental effects for the early stages of thyroid autoimmunity: a study of healthy Danish twins. *European Journal of Endocrinology* 2006 **154** 29–38. (<https://doi.org/10.1530/eje.1.02060>)
- Strieder TGA, Tijssen JGP, Wenzel BE, Endert E & Wiersinga WM. Prediction of progression to overt hypothyroidism or hyperthyroidism in female relatives of patients with autoimmune thyroid disease using the thyroid events Amsterdam (THEA) score. *Archives of Internal Medicine* 2008 **168** 1657–1663. (<https://doi.org/10.1001/archinte.168.15.1657>)
- Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H & Tunbridge F. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clinical Endocrinology* 1995 **43** 55–68. (<https://doi.org/10.1111/j.1365-2265.1995.tb01894.x>)
- Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ & O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 1095–1104. (<https://doi.org/10.1210/jc.2009-1977>)
- Åsvold BO, Vatten LJ, Midthjell K & Bjørø T. Serum TSH within the reference range as a predictor of future hypothyroidism and hyperthyroidism: 11-year follow-up of the HUNT study in Norway. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 93–99. (<https://doi.org/10.1210/jc.2011-1724>)
- Feldt-Rasmussen U, Bliddal S, Rasmussen AK, Boas M, Hilsted L & Main K. Challenges in interpretation of thyroid function tests in pregnant women with autoimmune thyroid disease. *Journal of Thyroid Research* 2011 **2011** 598712. (<https://doi.org/10.4061/2011/598712>)
- Vestergaard P. Smoking and thyroid disorders – a meta-analysis. *European Journal of Endocrinology* 2002 **146** 153–161. (<https://doi.org/10.1530/eje.0.1460153>)
- Belin RM, Astor BC, Powe NR & Ladenson PW. Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the third national health and nutrition examination survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 6077–6086. (<https://doi.org/10.1210/jc.2004-0431>)
- Carlé A, Bülow Pedersen I, Knudsen N, Perrild H, Ovesen L, Banke Rasmussen L, Jørgensen T & Laurberg P. Smoking cessation is followed by a sharp but transient rise in the incidence of overt

- autoimmune hypothyroidism – a population-based, case-control study. *Clinical Endocrinology* 2012 **77** 764–772. (<https://doi.org/10.1111/j.1365-2265.2012.04455.x>)
- 21 Åsvold BO, Bjørø T, Nilsen TIL & Vatten LJ. Tobacco smoking and thyroid function: a population-based study. *Archives of Internal Medicine* 2007 **167** 1428–1432. (<https://doi.org/10.1001/archinte.167.13.1428>)
 - 22 Effraïmidis G, Tijssen JGP & Wiersinga WM. Discontinuation of smoking increases the risk for developing thyroid peroxidase antibodies and/or thyroglobulin antibodies: a prospective study. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1324–1328. (<https://doi.org/10.1210/jc.2008-1548>)
 - 23 Carlé A, Bülow Pedersen I, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Jørgensen T & Laurberg P. Graves' hyperthyroidism and moderate alcohol consumption: evidence for disease prevention. *Clinical Endocrinology* 2013 **79** 111–119. (<https://doi.org/10.1111/cen.12106>)
 - 24 Effraïmidis G, Tijssen JGP & Wiersinga WM. Alcohol consumption as a risk factor for autoimmune thyroid disease: a prospective study. *European Thyroid Journal* 2012 **1** 99–104. (<https://doi.org/10.1159/000338920>)
 - 25 Carlé A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Jørgensen T & Laurberg P. Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case-control study. *European Journal of Endocrinology* 2012 **167** 483–490. (<https://doi.org/10.1530/EJE-12-0356>)
 - 26 Effraïmidis G, Strieder TGA, Tijssen JGP & Wiersinga WM. Natural history of the transition from euthyroidism to overt autoimmune hypo- or hyperthyroidism: a prospective study. *European Journal of Endocrinology* 2011 **164** 107–113. (<https://doi.org/10.1530/EJE-10-0785>)
 - 27 Falgarone G, Heshmati HM, Cohen R & Reach G. Mechanisms in Endocrinology: role of emotional stress in the pathophysiology of Graves' disease. *European Journal of Endocrinology* 2013 **168** R13–R18. (<https://doi.org/10.1530/EJE-12-0539>)
 - 28 Effraïmidis G, Tijssen JGP, Brosschot JF & Wiersinga WM. Involvement of stress in the pathogenesis of autoimmune thyroid disease: a prospective study. *Psychoneuroendocrinology* 2012 **37** 1191–1198. (<https://doi.org/10.1016/j.psyneuen.2011.12.009>)
 - 29 Kim D. The role of vitamin D in thyroid diseases. *International Journal of Molecular Sciences* 2017 **18** 1949.
 - 30 Effraïmidis G, Badenhop K, Tijssen JGP & Wiersinga WM. Vitamin D deficiency is not associated with early stages of thyroid autoimmunity. *European Journal of Endocrinology* 2012 **167** 43–48. (<https://doi.org/10.1530/EJE-12-0048>)
 - 31 van Zuuren EJ, Albusta AY, Fedorowicz Z, Carter B & Pijl H. Selenium supplementation for Hashimoto's thyroiditis: summary of a Cochrane systematic review. *European Thyroid Journal* 2014 **3** 25–31. (<https://doi.org/10.1159/000356040>)
 - 32 Kahaly GJ, Riedl M, König J, Diana T & Schomburg L. Double-blind, placebo-controlled, randomized trial of selenium in Graves hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 4333–4341. (<https://doi.org/10.1210/jc.2017-01736>)
 - 33 Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, Altea MA, Nardi M, Pitz S, Boboridis K *et al.* Selenium and the course of mild Graves' orbitopathy. *New England Journal of Medicine* 2011 **364** 1920–1931. (<https://doi.org/10.1056/NEJMoa1012985>)
 - 34 Negro R, Greco G, Mangieri T, Pezzarossa A, Dazzi D & Hassan H. The influence of selenium supplementation on postpartum thyroid status in pregnant women with thyroid peroxidase autoantibodies. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 1263–1268. (<https://doi.org/10.1210/jc.2006-1821>)
 - 35 Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K & Pearce SH. 2018 European Thyroid Association guideline for the management of Graves' hyperthyroidism. *European Thyroid Journal* 2018 **7** 167–186. (<https://doi.org/10.1159/000490384>)
 - 36 Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN *et al.* 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* 2016 **26** 1343–1421. (<https://doi.org/10.1089/thy.2016.0229>)
 - 37 Brito JP, Castaneda-Guarderas A, Gionfriddo MR, Singh Ospina NS, Maraka S, Dean DS, Castro MR, Fatourechi V, Gharib H, Stan MN *et al.* Development and pilot testing of an encounter tool for shared decision making about the treatment of Graves' disease. *Thyroid* 2015 **25** 1191–1198. (<https://doi.org/10.1089/thy.2015.0277>)
 - 38 Solomon DH, Beck JC & Vanderlaan WP. Prognosis of hyperthyroidism treated by antithyroid drugs. *JAMA* 1953 **152** 201–205. (<https://doi.org/10.1001/jama.1953.03690030001001>)
 - 39 Vitti P, Rago T, Chiovato L, Pallini S, Santini F, Fiore E, Rocchi R, Martino E & Pinchera A. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. *Thyroid* 1997 **7** 369–375. (<https://doi.org/10.1089/thy.1997.7.369>)
 - 40 Okamoto Y, Tanigawa SI, Ishikawa K & Hamada N. TSH receptor antibody measurements and prediction of remission in Graves' disease patients treated with minimum maintenance doses of antithyroid drugs. *Endocrine Journal* 2006 **53** 467–472. (<https://doi.org/10.1507/endocrj.K05-121>)
 - 41 Schleusener H, Schwander J, Fischer C, Holle R, Holl G, Badenhop K, Hensen J, Finke R, Bogner U & Mayr WR. Prospective multicentre study on the prediction of relapse after antithyroid drug treatment in patients with Graves' disease. *Acta Endocrinologica* 1989 **120** 689–701. (<https://doi.org/10.1530/acta.0.1200689>)
 - 42 Allahabadi A, Daykin J, Holder RL, Sheppard MC, Gough SC & Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 1038–1042. (<https://doi.org/10.1210/jcem.85.3.6430>)
 - 43 Daumerie C & Orgiazzi J. Reflections on the management of Graves' hyperthyroidism. *European Thyroid Journal* 2018 **7** 165–166. (<https://doi.org/10.1159/000491585>)
 - 44 Struja T, Fehlberg H, Kutz A, Guebelin L, Degen C, Mueller B & Schuetz P. Can we predict relapse in Graves' disease? Results from a systematic review and meta-analysis. *European Journal of Endocrinology* 2017 **176** 87–97. (<https://doi.org/10.1530/EJE-16-0725>)
 - 45 Vos XG, Ender E, Zwinderman AH, Tijssen JGP & Wiersinga WM. Predicting the risk of recurrence before the start of antithyroid drug therapy in patients with Graves' hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 1381–1389. (<https://doi.org/10.1210/jc.2015-3644>)
 - 46 Mazza E, Carlini M, Flecchia D, Blatto A, Zuccarini O, Gamba S, Beninati S & Messina M. Long-term follow-up of patients with hyperthyroidism due to Graves' disease treated with methimazole. Comparison of usual treatment schedule with drug discontinuation vs continuous treatment with low methimazole doses: a retrospective study. *Journal of Endocrinological Investigation* 2008 **31** 866–872. (<https://doi.org/10.1007/BF03346433>)
 - 47 Yamada T, Aizawa T, Koizumi Y, Komiya I, Ichikawa K & Hashizume K. Age-related therapeutic response to antithyroid drug in patients with hyperthyroid Graves' disease. *Journal of the American Geriatrics Society* 1994 **42** 513–516. (<https://doi.org/10.1111/j.1532-5415.1994.tb04973.x>)
 - 48 Winsa B, Dahlberg A, Jansson R, Agren H & Karlsson FA. Factors influencing the outcome of thyrostatic drug therapy in Graves' disease. *Acta Endocrinologica* 1990 **122** 722–728. (<https://doi.org/10.1530/acta.0.1220722>)
 - 49 Kimball LE, Kulinskaya E, Brown B, Johnston C & Farid NR. Does smoking increase relapse rates in Graves' disease? *Journal of Endocrinological Investigation* 2002 **25** 152–157. (<https://doi.org/10.1007/BF03343979>)
 - 50 Nedrebo BG, Holm PI, Uhlving S, Sorheim JI, Skeie S, Eide GE, Husebye ES, Lien EA & Aanderud S. Predictors of outcome and

Review	G Effraimidis	Predictive scores in AITD	181:3	R130
--------	---------------	---------------------------	-------	------

- comparison of different drug regimens for the prevention of relapse in patients with Graves' disease. *European Journal of Endocrinology* 2002 **147** 583–589. (<https://doi.org/10.1530/eje.0.1470583>)
- 51 Wang PW, Chen IY, Juo SHH, Hsi E, Liu RT & Hsieh CJ. Genotype and phenotype predictors of relapse of Graves' disease after antithyroid drug withdrawal. *European Thyroid Journal* 2013 **1** 251–258. (<https://doi.org/10.1159/000342621>)
 - 52 Eckstein AK, Lax H, Löscher C, Glowacka D, Plicht M, Mann K, Esser J & Morgenthaler NG. Patients with severe Graves' ophthalmopathy have a higher risk of relapsing hyperthyroidism and are unlikely to remain in remission. *Clinical Endocrinology* 2007 **67** 607–612. (<https://doi.org/10.1111/j.1365-2265.2007.02933.x>)
 - 53 Anagnostis P, Adamidou F, Polyzos SA, Katergari S, Karathanasi E, Zouli C, Panagiotou A & Kita M. Predictors of long-term remission in patients with Graves' disease: a single center experience. *Endocrine* 2013 **44** 448–453. (<https://doi.org/10.1007/s12020-013-9895-0>)
 - 54 Glaser NS, Styne DM & Organization of Pediatric Endocrinologists of Northern California Collaborative Graves' Disease Study Group. Predicting the likelihood of remission in children with Graves' disease: a prospective, multicenter study. *Pediatrics* 2008 **121** e481–e488. (<https://doi.org/10.1542/peds.2007-1535>)
 - 55 Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P & Léger J. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 3817–3826. (<https://doi.org/10.1210/jc.2008-0842>)
 - 56 Léger J, Gelwane G, Kaguelidou F, Benmerad M & Alberti C. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 110–119. (<https://doi.org/10.1210/jc.2011-1944>)
 - 57 Marinò M, Latrofa F, Menconi F, Chiovato L & Vitti P. Role of genetic and non-genetic factors in the etiology of Graves' disease. *Journal of Endocrinological Investigation* 2015 **38** 283–294. (<https://doi.org/10.1007/s40618-014-0214-2>)
 - 58 Struja T, Kaeslin M, Boesiger F, Jutzi R, Imahorn N, Kutz A, Bernasconi L, Mundwiler E, Mueller B, Christ-Crain M *et al.* External validation of the great score to predict relapse risk in Graves' disease: results from a multicenter, retrospective study with 741 patients. *European Journal of Endocrinology* 2017 **176** 413–419. (<https://doi.org/10.1530/EJE-16-0986>)
 - 59 Masiello E, Veronesi G, Gallo D, Premoli P, Bianconi E, Rosetti S, Cusini C, Sabatino J, Ippolito S, Piantanida E *et al.* Antithyroid drug treatment for Graves' disease: baseline predictive models of relapse after treatment for a patient-tailored management. *Journal of Endocrinological Investigation* 2018 **26** 1–8.
 - 60 Lazarus JH. Epidemiology of Graves' orbitopathy (GO) and relationship with thyroid disease. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2012 **26** 273–279. (<https://doi.org/10.1016/j.beem.2011.10.005>)
 - 61 Bartalena L, Pinchera A & Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. *Endocrine Reviews* 2000 **21** 168–199. (<https://doi.org/10.1210/edrv.21.2.0393>)
 - 62 Perros P & Kendall-Taylor P. Natural history of thyroid eye disease. *Thyroid* 1998 **8** 423–425. (<https://doi.org/10.1089/thy.1998.8.423>)
 - 63 Marcocci C, Bartalena L, Bogazzi F, Panicucci M & Pinchera A. Studies on the occurrence of ophthalmopathy in Graves' disease. *Acta Endocrinologica* 1989 **120** 473–478. (<https://doi.org/10.1530/acta.0.1200473>)
 - 64 Wiersinga W, Žarković M, Bartalena L, Donati S, Perros P, Okosieme O, Morris D, Fichter N, Lareida J, von G *et al.* Predictive score for the development or progression of Graves' orbitopathy in patients with newly diagnosed Graves' hyperthyroidism. *European Journal of Endocrinology* 2018 **178** 635–643. (<https://doi.org/10.1530/EJE-18-0039>)
 - 65 Mohaseb K, Linder M, Rootman J, Wilkins GE, Schechter MT, Dolman PJ & Singer J. Development and validation of a patient symptom questionnaire to facilitate early diagnosis of thyroid-associated orbitopathy in Graves' disease. *Orbit* 2008 **27** 419–425. (<https://doi.org/10.1080/01676830802414566>)
 - 66 Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, Pariani N, Gallo D, Azzolini C, Ferrario M *et al.* Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed Graves' hyperthyroidism seen at a single center. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 1443–1449. (<https://doi.org/10.1210/jc.2012-3873>)
 - 67 Perros P, Crombie AL, Matthews JN & Kendall-Taylor P. Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid-eye clinic. *Clinical Endocrinology* 1993 **38** 367–372. (<https://doi.org/10.1111/j.1365-2265.1993.tb00516.x>)
 - 68 Khong JJ, Finch S, De C, Rylander S, Craig JE, Selva D & Ebeling PR. Risk factors for Graves' orbitopathy; the Australian Thyroid-Associated Orbitopathy Research (ATOR) study. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 2711–2720. (<https://doi.org/10.1210/jc.2015-4294>)
 - 69 Manji N, Carr-Smith JD, Boelaert K, Allahabadia A, Armitage M, Chatterjee VK, Lazarus JH, Pearce SHS, Vaidya B, Gough SC *et al.* Influences of age, gender, smoking, and family history on autoimmune thyroid disease phenotype. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 4873–4880. (<https://doi.org/10.1210/jc.2006-1402>)
 - 70 Laurberg P, Berman DC, Bülow Pedersen I, Andersen S & Carlé A. Incidence and clinical presentation of moderate to severe Graves' orbitopathy in a Danish population before and after iodine fortification of salt. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2325–2332. (<https://doi.org/10.1210/jc.2012-1275>)
 - 71 Stein JD, Childers D, Gupta S, Talwar N, Nan B, Lee BJ, Smith TJ & Douglas R. Risk factors for developing thyroid-associated ophthalmopathy among individuals with Graves disease. *JAMA Ophthalmology* 2015 **133** 290–296. (<https://doi.org/10.1001/jamaophthalmol.2014.5103>)
 - 72 Vos XG, Smit N, Ender E, Tijssen JGP & Wiersinga WM. Frequency and characteristics of TBII-seronegative patients in a population with untreated Graves hyperthyroidism: a prospective study. *Clinical Endocrinology* 2008 **69** 311–317. (<https://doi.org/10.1111/j.1365-2265.2008.03192.x>)
 - 73 Lytton SD, Ponto KA, Kanitz M, Matheis N, Kohn LD & Kahaly GJ. A novel thyroid stimulating immunoglobulin bioassay is a functional indicator of activity and severity of Graves' orbitopathy. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 2123–2131. (<https://doi.org/10.1210/jc.2009-2470>)
 - 74 Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, Heckmann C, Esser J & Morgenthaler NG. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3464–3470. (<https://doi.org/10.1210/jc.2005-2813>)
 - 75 Gerding MN, van der Meer JW, Broenink M, Bakker O, Wiersinga WM & Prummel MF. Association of thyrotrophin receptor antibodies with the clinical features of Graves' ophthalmopathy. *Clinical Endocrinology* 2000 **52** 267–271. (<https://doi.org/10.1046/j.1365-2265.2000.00959.x>)
 - 76 Tallstedt L, Lundell G, Törring O, Wallin G, Ljunggren JG, Blomgren H & Taube A. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. *New England Journal of Medicine* 1992 **326** 1733–1738. (<https://doi.org/10.1056/NEJM199206253262603>)
 - 77 Träisk F, Tallstedt L, Abraham-Nordling M, Andersson T, Berg G, Calissendorff J, Hallengren B, Hedner P, Lantz M, Nyström E *et al.* Thyroid-associated ophthalmopathy after treatment for Graves'

- hyperthyroidism with antithyroid drugs or iodine-131. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 3700–3707. (<https://doi.org/10.1210/jc.2009-0747>)
- 78 Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, Perros P, Salvi M, Wiersinga WM & European Group on Graves' Orbitopathy (EUGOGO). The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *European Thyroid Journal* 2016 **5** 9–26. (<https://doi.org/10.1159/000443828>)
 - 79 Prummel M, Wiersinga W, Mourits MP, Koornneef L, Berghout A & van der Gaag R. Amelioration of eye changes of Graves' ophthalmopathy by achieving euthyroidism. *Acta Endocrinologica* 1989 **121** 185–190.
 - 80 Tallstedt L, Lundell G, Blomgren H & Bring J. Does early administration of thyroxine reduce the development of Graves' ophthalmopathy after radioiodine treatment? *European Journal of Endocrinology* 1994 **130** 494–497. (<https://doi.org/10.1530/eje.0.1300494>)
 - 81 Kung AW, Yau CC & Cheng A. The incidence of ophthalmopathy after radioiodine therapy for Graves' disease: prognostic factors and the role of methimazole. *Journal of Clinical Endocrinology and Metabolism* 1994 **79** 542–546. (<https://doi.org/10.1210/jcem.79.2.7913934>)
 - 82 Hegedüs L, Bonnema SJ, Smith TJ & Brix TH. Treating the thyroid in the presence of Graves' ophthalmopathy. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2012 **26** 313–324. (<https://doi.org/10.1016/j.beem.2011.09.005>)
 - 83 Bartalena L. The dilemma of how to manage Graves' hyperthyroidism in patients with associated orbitopathy. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 592–599. (<https://doi.org/10.1210/jc.2010-2329>)
 - 84 Bednarczuk T, Gopinath B, Ploski R & Wall JR. Susceptibility genes in Graves' Ophthalmopathy: searching for a needle in a haystack? *Clinical Endocrinology* 2007 **67** 3–19. (<https://doi.org/10.1111/j.1365-2265.2007.02854.x>)
 - 85 Villanueva R, Inzerillo AM, Tomer Y, Barbesino G, Meltzer M, Concepcion ES, Greenberg DA, MacLaren N, Sun ZS, Zhang DM *et al.* Limited genetic susceptibility to severe Graves' ophthalmopathy: no role for CTLA-4 but evidence for an environmental etiology. *Thyroid* 2000 **10** 791–798. (<https://doi.org/10.1089/thy.2000.10.791>)
 - 86 Khong JJ, Burdon KP, Lu Y, Leonards L, Laurie KJ, Walsh JP, Gajdatsy AD, Ebeling PR, McNab AA, Hardy TG *et al.* Association of polymorphisms in MACRO domain containing 2 with thyroid-associated orbitopathy. *Investigative Ophthalmology and Visual Science* 2016 **57** 3129–3137. (<https://doi.org/10.1167/iovs.15-18797>)
 - 87 Andersen S, Pedersen KM, Bruun NH & Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 1068–1072. (<https://doi.org/10.1210/jcem.87.3.8165>)
 - 88 Ankrah-Tetteh T, Wijeratne S & Swaminathan R. Intraindividual variation in serum thyroid hormones, parathyroid hormone and insulin-like growth factor-1. *Annals of Clinical Biochemistry* 2008 **45** 167–169. (<https://doi.org/10.1258/acb.2007.007103>)
 - 89 Meikle AW, Stringham JD, Woodward MG & Nelson JC. Hereditary and environmental influences on the variation of thyroid hormones in normal male twins. *Journal of Clinical Endocrinology and Metabolism* 1988 **66** 588–592. (<https://doi.org/10.1210/jcem-66-3-588>)
 - 90 Bufalo NE, Santos RB, Cury AN, Andrade RA, Morari J, Morari EC, Leite JL, Monte O, Romaldini JH & Ward LS. Genetic polymorphisms associated with cigarette smoking and the risk of Graves' disease. *Clinical Endocrinology* 2008 **68** 982–987. (<https://doi.org/10.1111/j.1365-2265.2007.03121.x>)
 - 91 Beumer W, Effraimidis G, Drexhage RC, Wiersinga WM & Drexhage HA. Changes in serum adhesion molecules, chemokines, cytokines, and tissue remodeling factors in euthyroid women without thyroid antibodies who are at risk for autoimmune thyroid disease: a hypothesis on the early phases of the endocrine autoimmune reaction. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 2460–2468. (<https://doi.org/10.1210/jc.2012-4122>)
 - 92 Massolt ET, Effraimidis G, Korevaar TIM, Wiersinga WM, Visser WE, Peeters RP & Drexhage HA. Aberrant levels of hematopoietic/neuronal growth and differentiation factors in euthyroid women at risk for autoimmune thyroid disease. *PLoS ONE* 2016 **11** e0153892. (<https://doi.org/10.1371/journal.pone.0153892>)
 - 93 Opazo MC, Ortega-Rocha EM, Coronado-Arrázola I, Bonifaz LC, Boudin H, Neunlist M, Bueno SM, Kalergis AM & Riedel CA. Intestinal microbiota influences non-intestinal related autoimmune diseases. *Frontiers in Microbiology* 2018 **9** 432. (<https://doi.org/10.3389/fmicb.2018.00432>)
 - 94 Knip M & Siljander H. The role of the intestinal microbiota in type 1 diabetes mellitus. *Nature Reviews: Endocrinology* 2016 **12** 154–167. (<https://doi.org/10.1038/nrendo.2015.218>)
 - 95 Köhling HL, Plummer SF, Marchesi JR, Davidge KS & Ludgate M. The microbiota and autoimmunity: their role in thyroid autoimmune diseases. *Clinical Immunology* 2017 **183** 63–74. (<https://doi.org/10.1016/j.clim.2017.07.001>)
 - 96 Walsh SJ & Rau LM. Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States. *American Journal of Public Health* 2000 **90** 1463–1466. (<https://doi.org/10.2105/ajph.90.9.1463>)
 - 97 McLachlan SM & Rapoport B. Breaking tolerance to thyroid antigens: changing concepts in thyroid autoimmunity. *Endocrine Reviews* 2014 **35** 59–105. (<https://doi.org/10.1210/er.2013-1055>)

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