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.

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

Grigoris Effraimidis is an endocrinologist at the Department of Medical Endocrinology in the Rigshospitalet University Hospital, Copenhagen, Denmark. He graduated from the University of Thessaly Medical School in Greece and he obtained his PhD from the University of Amsterdam. His research interests are thyroid diseases with a particular focus on AITDs. Recently, he has been involved in research projects related to Fabry disease.
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 (4.8) 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 hypoor 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 TBI (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 2.0mU/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
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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 (\( \lambda_s \)) 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 Whickham 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 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).

### Table 1 Calculation and risk stratification of the Thyroid Hormones Event Amsterdam (THEA) score.

<table>
<thead>
<tr>
<th>RR (%)</th>
<th>Hypothyroid event</th>
<th>Hyperthyroid event</th>
<th>Any event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low: 0–7</td>
<td>2.6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Medium: 8–10</td>
<td>13.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High: 11–15</td>
<td>32.9</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Very high: 16–21</td>
<td>59.4</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Calculation of scores

- **TSH, mU/L**
  - <0.4: 0
  - 0.4–2.0: 0
  - 2.1–4.0: 3
  - 4.1–5.7: 6
  - >5.7: 9

- **TPO antibodies, kU/L**
  - <100: 0
  - 100–1000: 3
  - 1001–10,000: 6
  - >10,000: 9

- **Family background**
  - 2 relatives with Graves’: 0
  - 2 relatives with Hashimoto: 3

Maximum score: 21

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

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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...

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**Table 2** Predictive scores in AITD. Utility, applicable populations, modifiable and non-modifiable predictor factors and determinants.

<table>
<thead>
<tr>
<th>Utility population</th>
<th>THEA score</th>
<th>GREAT score</th>
<th>PREDIGO score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimation of the risk of the development of overt AITD in females with first- or second-degree relatives of AITD patients</strong></td>
<td><strong>Estimation of the risk of recurrence of GH after ATDs discontinuation in newly diagnosed GH patients</strong></td>
<td><strong>Estimation of the risk of the development of GO in newly diagnosed GH patients without overt GO undergoing ATDs treatment</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Predictive factors involved in the score</strong></td>
<td><strong>Predictive factors involved in the score</strong></td>
<td><strong>Predictive factors involved in the score</strong></td>
<td></td>
</tr>
<tr>
<td>TSH levels</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>TPOAb levels</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>Family history</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>fT4 levels</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>Age</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>TBII levels</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>Goiter size</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>Duration of hyperthyroid symptoms</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>Genetic polymorphisms</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>CAS score</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non-modifiable</td>
<td>Modifiable? Doesn’t change risk of HH. Increases risk of GH</td>
<td>Modifiable. Increases risk of HH.</td>
</tr>
<tr>
<td><strong>Determinants NOT involved in the score</strong></td>
<td><strong>Determinants NOT involved in the score</strong></td>
<td><strong>Determinants NOT involved in the score</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Modifiable. Decreases risk of HH. Increases risk of GH</td>
<td>Modifiable. Possible risk factor for recurrence</td>
<td>Modifiable. Increases risk of both HH and GH</td>
</tr>
<tr>
<td>Gender</td>
<td>Non-modifiable. Maybe risk factor for recurrence</td>
<td>Non-modifiable. Increases risk of GO males &gt; females</td>
<td>Non-modifiable. Older age is a risk factor for the development of GO</td>
</tr>
<tr>
<td>Age</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
<td>Non-modifiable</td>
</tr>
<tr>
<td>Moderate alcohol intake</td>
<td>Modifiable. Decreases risk of both HH and GH</td>
<td>Non-modifiable. May be risk factor for recurrence</td>
<td>Non-modifiable. Higher probability of GO with higher baseline T3</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Modifiable. Increases risk of both HH and GH</td>
<td>Non-modifiable. May be the risk for the development of GO males &gt; females</td>
<td>Non-modifiable. Higher probability of GO with higher baseline T3</td>
</tr>
<tr>
<td>Presence of Graves’ orbitopathy</td>
<td>Non-modifiable. Maybe risk factor for recurrence</td>
<td>Non-modifiable. May be the risk for the development of GO males &gt; females</td>
<td>Non-modifiable. Higher probability of GO with higher baseline T3</td>
</tr>
<tr>
<td>Biochemical severity of GH</td>
<td>Non-modifiable. May be the risk for the development of GO males &gt; females</td>
<td>Non-modifiable. May be the risk for the development of GO males &gt; females</td>
<td>Non-modifiable. Higher probability of GO with higher baseline T3</td>
</tr>
<tr>
<td>Stress</td>
<td>Non-modifiable. May be the risk for the development of GO males &gt; females</td>
<td>Non-modifiable. May be the risk for the development of GO males &gt; females</td>
<td>Non-modifiable. Higher probability of GO with higher baseline T3</td>
</tr>
<tr>
<td>Selenium</td>
<td>Modifiable. Decreases risk of both HH and GH</td>
<td>Modifiable. Decreases risk of both HH and GH</td>
<td>Modifiable. Decreases risk of both HH and GH</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Modifiable. Unknown effect, data still inconclusive</td>
<td>Modifiable. Unknown effect, data still inconclusive</td>
<td>Modifiable. Unknown effect, data still inconclusive</td>
</tr>
</tbody>
</table>

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.

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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 30 mg 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

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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 U/L: 0, 1 or 2 points), WHO grades for goiter (grade 0–1, 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 around 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.

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

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.

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, TBIll, 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 \( \geq 1 \) (Odds ratio, OR = 4.45 for CAS \( \geq 1 \)), current smoking (OR = 2.72), higher TBII level (OR = 3.75 for TBII level \( \geq 10 \text{U/L} \)) and duration of hyperthyroid symptoms (OR = 3.35 for duration \( > 4 \text{months} \)).

From the independent variables, a 15-point predictive score of GO, named Prediction of Graves’ Orbitopathy (PREDIGO), was constructed (Table 4). Scores \( \geq 6 \) have some predictive value for developing GO, while scores \( \leq 6 \) 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.

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

<table>
<thead>
<tr>
<th>Determinant</th>
<th>PREDIGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>( \geq 1 )</td>
<td>5</td>
</tr>
<tr>
<td>Serum TBII (IU/L)</td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>0</td>
</tr>
<tr>
<td>2–10</td>
<td>2</td>
</tr>
<tr>
<td>&gt;10</td>
<td>5</td>
</tr>
<tr>
<td>Duration of hyperthyroid symptoms (months)</td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>1–4</td>
<td>1</td>
</tr>
<tr>
<td>&gt;4</td>
<td>3</td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Maximum score</td>
<td>15</td>
</tr>
</tbody>
</table>

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

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**Table 5**  Possible future developments in the prediction of AITD.

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

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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