Thyroid and Islet Autoantibodies Predict Autoimmune Thyroid Disease at Type 1 Diabetes Diagnosis

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Context: Screening of autoimmune thyroid disease in children with type 1 diabetes is important but varies between clinics.

Objective: To determine the predictive value of thyroid autoantibodies, thyroid function, islet autoantibodies, and HLA-DQ at diagnosis of type 1 diabetes for autoimmune thyroid disease during follow-up.

Setting: Forty-three Swedish pediatric endocrinology units.

Design, Patients, and Main Outcome Measures: At diagnosis of type 1 diabetes, autoantibodies against thyroid peroxidase (TPOAb), thyroglobulin (TGAb), glutamic acid decarboxylase (GADA), insulin, insulinoma-associated protein-2, and 3 variants of zinc transporter 8 (ZnT8W/R/QA) *HLA-DQA1-B1* genotypes and thyroid function were analyzed in 2433 children. After 5.1 to 9.5 years, information on thyroxine treatment was gathered from the Swedish National Board of Health and Welfare's Prescribed Drug Register.

Results: Thyroxine was prescribed to 6% of patients. In patients <5 years of age, female sex [hazard ratio (HR) = 4.60; $P = 0.008$] and GADA (HR = 5.80; $P = 0.02$) were predictors. In patients 5 to 10 years old, TPOAb (HR = 20.56; $P < 0.0001$), TGAb (HR = 3.40; $P = 0.006$), and thyroid-stimulating hormone (TSH) (HR = 3.64; $P < 0.001$) were predictors, whereas in 10 to 15 year olds, TPOAb (HR = 17.00; $P < 0.001$) and TSH (HR = 4.11; $P < 0.001$) predicted thyroxine prescription.

Conclusion: In addition to TPOAb and TSH, GADA at diagnosis of type 1 diabetes is important for the prediction of autoimmune thyroid disease in children <5 years of age. (***J Clin Endocrinol Metab*** **102: 1277–1285, 2017)**

Thyroid autoimmunity and autoimmune thyroid disease are frequently associated with type 1 diabetes (1), possibly because of a common genetic predisposition (2). The immune-mediated destruction is thought to be triggered by environmental factors in genetically susceptible individuals. The disease is characterized by infiltration of the thyroid gland by T and B lymphocytes as well as macrophages and dendritic cells, reflected by autoantibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TGAb). The predictive value of thyroid autoantibodies for autoimmune thyroid disease is high (3–6).

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*Members of the Better Diabetes Diagnosis study group are listed in the Appendix. Abbreviations: CI, confidence interval; GADA, autoantibodies to glutamic acid decarboxylase; HR, hazard ratio; IA-2A, autoantibodies to insulinoma-associated protein-2; IAA, autoantibodies to insulin; TGAb, autoantibodies to thyroglobulin; TPOAb, autoantibodies to thyroid peroxidase; TSH, thyroid-stimulating hormone; ZnT8, zinc transporter 8.

Autoimmune thyroid disease can present as either hypothyroidism or hyperthyroidism, hypothyroidism being far more common. The clinical symptoms of hypothyroidism are vague, and children and adolescents may go undiagnosed. Hypothyroidism in type 1 diabetes is related to dyslipidemia and coronary heart disease (7, 8). Despite the fact that early detection of autoimmune thyroid disease is needed, the recommendations on screening for this disease in children and young adults with type 1 diabetes vary.

We previously reported that thyroid autoantibodies were associated with autoantibodies to glutamic acid decarboxylase (GADA) and zinc transporter 8 (ZnT8A) and negatively associated with *HLA-DQB1*05:01* (9). In this study, we used our unique nationwide cohort of 2433 newly diagnosed type 1 diabetes patients and linked it to the Swedish National Board of Health and Welfare's Prescribed Drug Register to study prescription of thyroxine as a measure of clinically diagnosed autoimmune thyroid disease. The aims were to determine the predictive value of thyroid and islet autoantibodies as well as thyroid function parameters and *HLA-DQ* genotype at the time of type 1 diabetes diagnosis for development of autoimmune hypothyroid disease and to evaluate whether our previous findings on thyroid autoimmunity could be extended to autoimmune hypothyroid disease.

Material and Methods

Subjects

Blood samples were collected from Swedish children and adolescents (n = 2670) at diagnosis of type 1 diabetes between May 2005 and October 2009 in the Better Diabetes Diagnosis study, which included >90% of all incident cases of type 1 diabetes in children <18 years of age in Sweden (10). Patients with type 2 diabetes (n = 57), secondary diabetes (n = 32), neonatal diabetes (n = 3), MODY (n = 27), or unknown type of diabetes (n = 46) were excluded. After exclusion of 237 children with missing data (of the total 2670 children with type 1 diabetes), 2433 remained. Data on thyroxine prescription were obtained from the Swedish National Board of Health and Welfare's Prescribed Drug Register (http://www.socialstyrelsen.se/english) and were used to define the outcome of autoimmune thyroid disease. The regional ethics review board of Lund approved the study.

Autoantibodies to thyroid peroxidase and thyroglobulin

TPOAb (kit No. L2KTO2) and TGAb (kit No. L2KTG2) were determined in serum samples using the Immulite® 2000 analyzer (Siemens Healthcare, Deerfield, IL) according to the manufacturer's instructions. Cutoffs for positive values were ≥36 U/mL for TPOAb and ≥41 U/mL for TGAb.

Autoantibodies to ZnT8 variants

The radio-binding assays for autoantibodies against each of the ZnT8R, ZnT8W, and ZnT8Q variants were performed as previously described (11, 12). The results were expressed in arbitrary units derived from in-house positive and negative standard samples. Cutoffs for positive values were ZnT8RA ≥65 U/mL, ZnT8WA ≥75 U/mL, and ZnT8QA ≥100 U/mL.

Autoantibodies to GAD and insulinoma-associated protein-2 (IA-2A)

The radio-binding assays for GADA and IA-2A were carried out as described (10). GADA and IA-2A levels were expressed as U/mL derived from the World Health Organization standard 97/550 (13, 14). Cutoffs for positive values were GADA ≥35 U/mL and IA-2A ≥6 U/mL.

Autoantibodies to insulin

The radio-binding assay for autoantibodies to insulin (IAA) was carried out as described (15). The results were expressed in arbitrary units derived from in-house standard samples. Samples were considered positive if IAA levels were ≥0.8 relative units.

Our laboratory is participating in the biannual Islet Autoantibody Standardization Program (http://www.immunologyofdiabetessociety.com/). Workshop sensitivity and specificity for islet autoantibodies in the Islet Autoantibody Standardization Program 2015 were as follows: GADA, 76% and 95.6%; IA-2A, 72% and 100%; IAA, 26% and 97.8%; ZnT8WA, 50% and 100%; ZnT8RA, 58%, and 100%; and ZnT8QA, 38% and 100%.

HLA genotyping

HLA-DQB1 and *DQA1* alleles were typed by sequence-specific oligonucleotide probes on dried blood spots used directly for PCR amplification of *DQA1* and *DQB1* alleles using the DELFIA Hybridization Assay (PerkinElmer, Boston, MA) as described (16).

TSH and free T_4

TSH and free T_4 in serum samples were analyzed using the Immulite® 2000 analyzer. Reference values were 0.4 to 3.5 mU/L for TSH and 12 to 22 pmol/L for free T_4.

Statistical methods

Statistical analyses were performed using SPSS statistical software (version 22.0; IBM SPSS, Armonk, NY) and R 3.1.1 (https://www.r-project.org/). Differences between groups were tested using the χ^2 test or Mann-Whitney *U* test depending on the variable. Association with future thyroxine prescription was analyzed with Cox proportional hazards modeling using the Survival package in R.

Results

In 2433 children, 56% boys (n = 1390) and 44% girls (n = 1073), with a median age of 10.3 years (range, 0.7 to 17.9 years) at diagnosis of type 1 diabetes, the Swedish National Board of Health and Welfare's Prescribed Drug Register indicated that 6% of patients (147/2433) had been prescribed thyroxine (66% girls) after 5.1 to 9.5 years (median, 7.3 years) of diabetes (Fig. 1). Of those, only 6.8% of patients (10/147) had been prescribed thyroxine before the diagnosis of type 1 diabetes (range, 4.3 years to 1 week before

diagnosis). These 10 patients were excluded from later prediction analysis.

Thyroxine prescription in relation to sex, age, and type 1 diabetes diagnosis

Thyroxine prescription was more common in girls (F to M ratio, 1.94:1). The age at thyroxine prescription varied between 3.6 and 25.7 years (median, 12.9 years). Children who were prescribed thyroxine were older (median, 11.4 years) at type 1 diabetes diagnosis than those not prescribed thyroxine (median, 10.1 years) ($P = 0.002$; Mann-Whitney U test). In the 421 children who were diagnosed with type 1 diabetes before 5 years of age (270 boys and 151 girls), 5% (19/421; 4 boys and

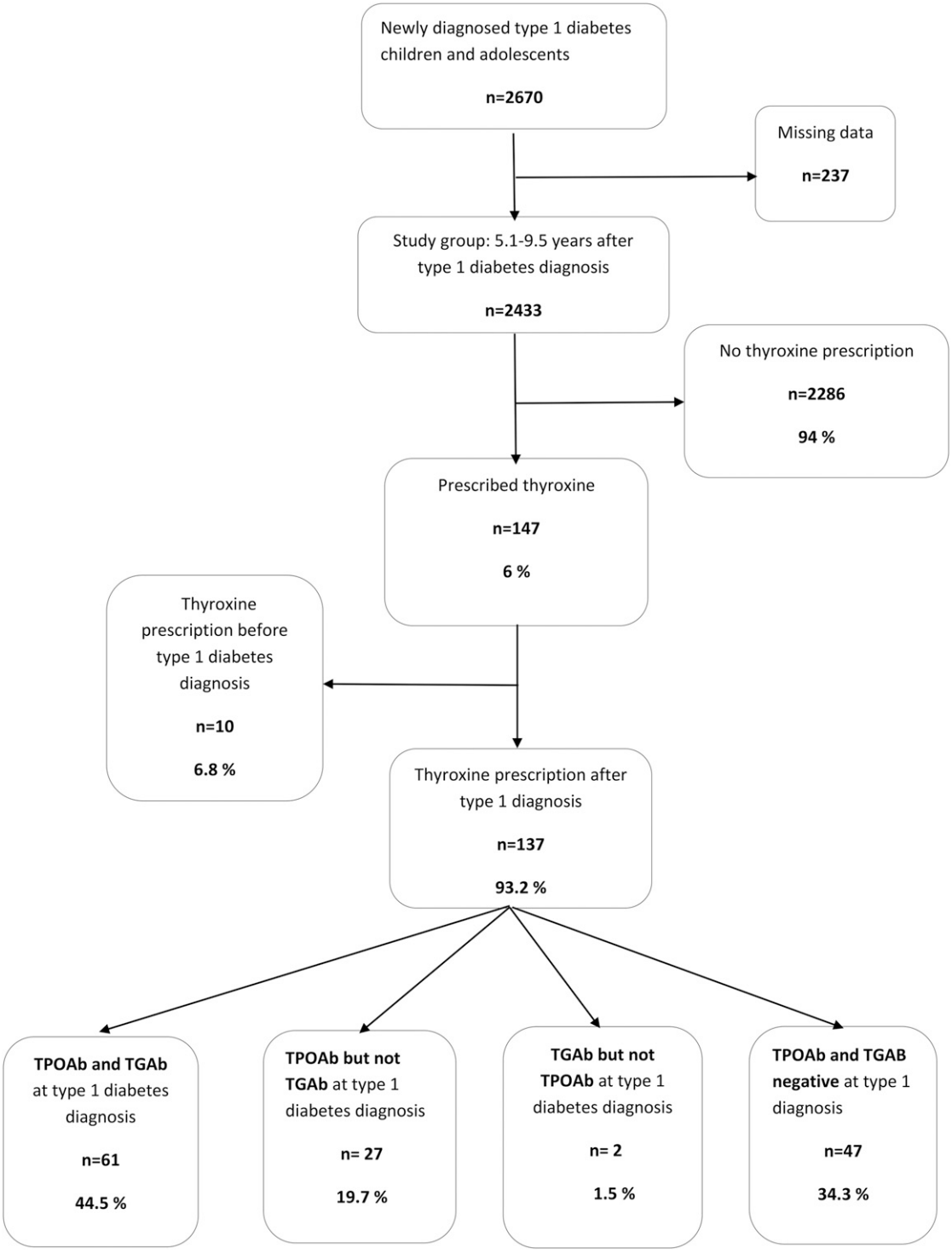

Figure 1. Flowchart of the study population in relation to thyroxine prescription, TPOAb, and TGAb.

15 girls) had been prescribed thyroxine after diagnosis of diabetes. The prescription of thyroxine in relation to time of type 1 diabetes diagnosis is shown in Figure 2.

Predictive value of TPOAb, TGAb, TSH, and free T_4 at type 1 diabetes diagnosis for future thyroxine prescription

At the time of type 1 diabetes diagnosis, 9% of patients (240/2423) were positive for TPOAb, and 8% (193/2423) for TGAb. Positive TPOAb (HR = 21.00; $P < 0.001$) and TGAb (HR = 11.83; $P < 0.001$) at the diagnosis of type 1 diabetes increased the risk for later thyroxine prescription [Fig. 3(A) and 3(B); Table 1]. In addition, the levels of TPOAb ($P < 0.001$; Mann-Whitney) but not TGAb ($P = 0.10$) in thyroid autoantibody–positive children were significantly higher in those who were prescribed thyroxine (mean, 740 U/mL) than in those who were not (mean, 317 U/mL) (Supplemental Figs. 1 and 2). TSH levels outside the reference limits were positively associated with future thyroxine prescription (HR = 4.57; $P < 0.001$) [Fig. 3(C); Table 1]. This was also observed for free T_4 in a univariate Cox model (HR = 1.82, 95% confidence interval [CI]: 1.20 to 2.78; $P = 0.005$) (Table 1).

Association of islet autoantibodies at type 1 diabetes diagnosis with future thyroxine prescription

GADA at diagnosis of type 1 diabetes increased the risk for later thyroxine prescription (HR = 2.84; $P < 0.001$) [Fig. 3(D); Table 1], whereas no association was found for IA-2A, IAA, or any of the 3 ZnT8As (R/W/Q) (Table 1). In TPOAb-negative patients, the risk of future thyroxine prescription was increased if GADA was positive; 3.0% of patients (41/1382) who were positive for GADA but negative for TPOAb were later prescribed thyroxine compared with 1.0% of patients (8/801) who were negative for both TPOAb and GADA ($P = 0.003$). In addition, higher levels of GADA in GADA-positive children were associated with future thyroxine prescription ($P = 0.013$; Mann-Whitney U test) (Supplemental Fig. 3).

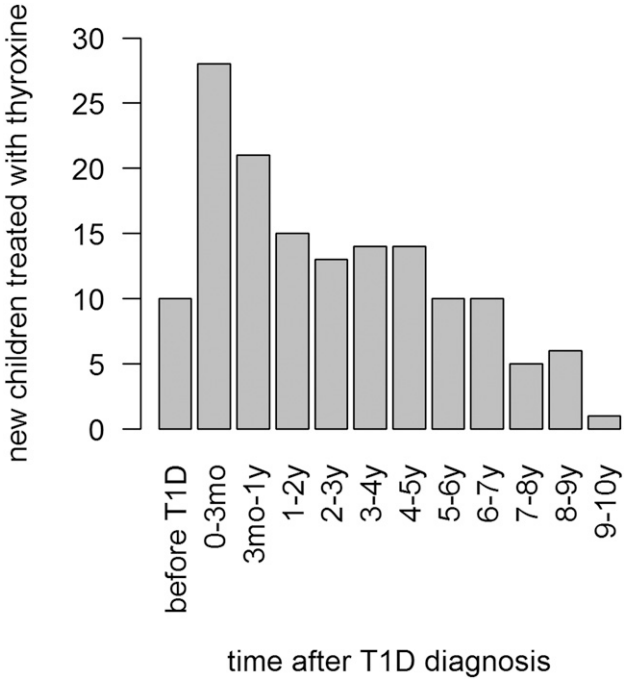

Figure 2. The prescription of thyroxine in relation to time of type 1 diabetes diagnosis. T1D, type 1 diabetes.

Combined predictive analyses of islet and thyroid autoantibodies and relation to age

Sex ($P = 0.03$), TPOAb level, ($P < 0.001$), TGAb level ($P = 0.02$), TSH level outside the reference limits ($P < 0.001$), and GADA ($P = 0.040$), but not age ($P = 0.10$) or free T_4 ($P = 0.10$), at type 1 diabetes diagnosis were all found to be independent predictive variables for future thyroxine prescription (Table 1).

Survival analysis (Kaplan-Meier) of the time to thyroxine prescription in children positive or negative for TPOAb and TSH values within or outside the reference limits illustrates the independence of the variables and that in TPOAb-positive children in particular, the risk was increased if TSH values were outside the reference limits [Fig. 3(E)]. It was also clear that patients who were positive for both TPOAb and GADA at type 1 diabetes diagnosis had an enhanced risk [Fig. 3(F)].

Although age was not an independent predictive variable, we wanted to examine the different predictors in relation to age at type 1 diabetes diagnosis, with special interest in those diagnosed when young. We therefore performed multivariate Cox modeling of sex, TPOAb, TGAb, TSH, and GADA in different age groups. In the youngest children, <5 years of age at type 1 diabetes diagnosis, female sex (HR = 4.64, CI: 1.49 to 14.45; $P = 0.008$) and positive GADA (HR = 5.79, CI: 1.32 to 25.42; $P = 0.02$) were the most important predictors for later thyroxine prescription. In the age group 5 to 10 years, positive TPOAb (HR = 20.56, CI: 8.39 to 50.35; $P < 0.001$), positive TGAb (HR = 3.39, CI: 1.42 to 8.13; $P = 0.006$), and TSH value outside the reference limits (HR = 3.64, CI: 1.72 to 7.69; $P < 0.001$) were the most important predictors, whereas positive TPOAb (HR = 17.00, CI: 8.40 to 34.44; $P < 0.001$) and TSH value outside the reference limits (HR = 4.11, CI: 2.41 to 7.03; $P < 0.001$) best predicted thyroxine prescription for patients 10 to 15 years (Fig. 4).

Only 7.3% of children (10/137) prescribed thyroxine after the diagnosis of type 1 diabetes were negative for TPOAb, TGAb, and GADA and had a TSH value within the reference limits at diagnosis of diabetes. One of these

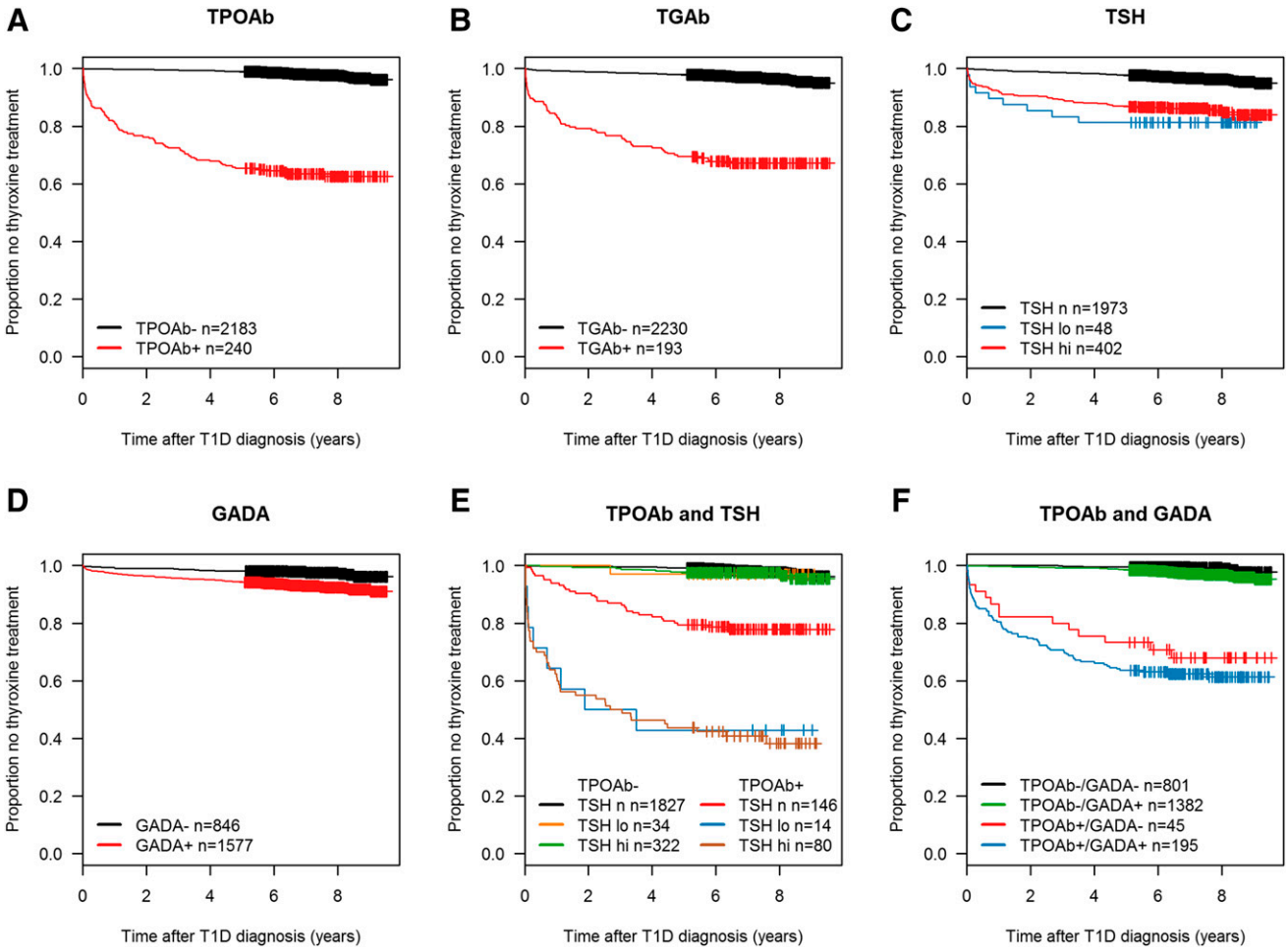

Figure 3. Kaplan-Meier curves with thyroxine prescription as end point grouped according to (A) TPOAb, (B) TGAb, (C) TSH outside the reference limits, (D) GADA, (E) TPOAb and TSH outside the reference limits, and (F) TPOAb and GADA at type 1 diabetes onset.

patients was prescribed thyroxine within 90 days of the type 1 diabetes diagnosis (age 15, M), another patient a year after (age 5, M), 3 patients 1 to 5 years after (age 12 [M], age 17 [F], and age 18 [M]), and 5 patients >5 years after type 1 diabetes diagnosis (age 17 [M], age 20 [F], age 20 [F], age 21 [F], and age 22 [F]).

The association between *HLA DQ* genotypes and thyroxine prescription

A negative association between *HLA-DQ* and future thyroxine prescription was found for genotypes containing the *DQA1*01:01-B1*05:01* ($P = 0.004$) *and DQA1*03:01-B1*03:02* ($P = 0.01$) haplotypes, in addition to the genotype

Table 1. Predictive Value of Age, Sex, TPOAb, TGAb, TSH, Free T_4, and Islet Autoantibodies at Type 1 Diabetes Diagnosis for Future Thyroxine Treatment

	Univariate Cox			Multivariate Cox		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Type 1 diabetes age, y	1.05	1.01–1.10	0.01	0.96	0.92–1.01	0.10
Sex	2.56	1.80–3.65	<0.001	1.49	1.03–2.15	0.03
TPOAb	21.00	14.80–29.80	<0.001	12.77	8.04–20.30	<0.001
TGAb	11.83	8.45–16.56	<0.001	1.65	1.07–2.53	0.02
TSH	4.57	3.27–6.39	<0.001	2.68	1.90–3.78	<0.001
Free T_4	1.82	1.20–2.78	0.005	1.43	0.94–2.20	0.10
GADA	2.84	1.80–4.48	<0.001	1.64	1.02–2.64	0.04
IA-2A	0.97	0.65–1.44	0.88			
IAA	1.35	0.96–1.89	0.08			
ZnT8RA	1.33	0.95–1.88	0.10			
ZnT8WA	1.05	0.75–1.46	0.80			
ZnT8QA	1.03	0.72–1.47	0.88			

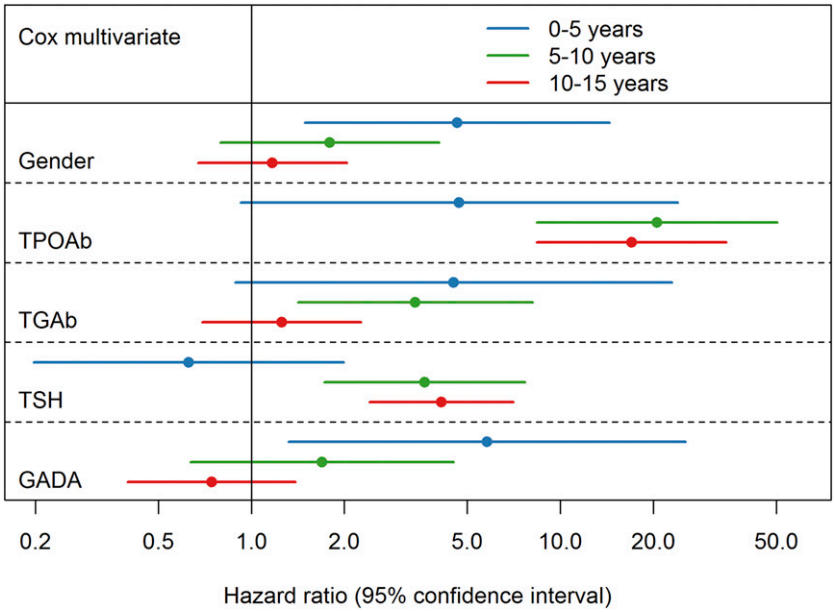

Figure 4. Combined predictive analyses of islet and thyroid autoantibodies and relation to age at type 1 diabetes diagnosis.

*DQA1*03:01-DQB1*03:02/DQA1*01:01-B1*05:01* (P = 0.03). No positive association was found for any haplotype or genotype.

Discussion

In our large cohort of 2433 children and adolescents, we found that thyroid and islet autoantibodies analyzed at the time of diagnosis of type 1 diabetes predicted prescription of thyroxine within 5 to 9 years. The predictive parameters differed considerably by age; female sex and positive GADA at onset of diabetes were of most importance in the youngest, whereas positive thyroid autoantibodies and TSH outside the reference interval at onset of disease were more important in older children. Our findings are of considerable significance because they indicate that autoimmune thyroid disease may be predicted already at the time of diagnosis of type 1 diabetes.

Guidelines to screen for autoimmune thyroid disease in type 1 diabetes vary regarding both frequency of testing and choice of test. These different recommendations are often based on frequency of autoimmune thyroid disease in fairly small studies, primarily not aimed at identifying predictive factors. At onset of diabetes, screening with TPOAb, TSH, and free T_4 is often recommended (2, 17, 18), whereas recommendations differ regarding follow-up. In patients who are positive for thyroid autoimmunity, screening with TSH (17, 19, 20) or TPOAb and TSH annually has been recommended (18, 21). Others recommend TSH 6 weeks after type 1 diabetes diagnosis and annual screening with TPOAb thereafter in those with abnormal TSH (22). The International Society for Pediatric and Adolescent Diabetes recommends screening with TSH and TPOAb at diagnosis of type 1 diabetes and every second year thereafter in asymptomatic individuals without goiter or in the absence of thyroid autoantibodies, whereas no specific recommendations are given on how children with thyroid autoimmunity should be followed up (23).

In our large study, we were able to identify predictive factors of autoimmune thyroid disease at onset of type 1 diabetes, which may help to increase precision in the screening programs. GADA has previously not been mentioned for the purpose of screening for autoimmune thyroid disease, although a relation between GADA and thyroid autoimmunity was previously described by us and others (9, 24). There may be 2 explanations for the association between GADA and autoimmune thyroid disease. The first is that GADA is co-occurring with TPOAb, TGAb, or both because the immunogenetic risk is shared between beta cell and thyroid autoimmunity. The other is that the trigger of beta cell and thyroid autoimmunity, such as an infectious agent, is shared. There is no evidence that GAD is expressed in thyrocytes.

Interestingly, Pilia *et al.* (25) found that 8% of nondiabetic children and adolescents with newly diagnosed autoimmune thyroid disease were positive for GADA and/or IA-2A. We did not find any relation with IA-2A and could not confirm our previous finding of a relation between autoantibodies against ZnT8 and thyroid autoimmunity in patients receiving thyroxine treatment (9). The explanation might be that there are different associations between islet autoimmunity in relation to thyroid autoimmunity and clinical thyroid disease.

GADA is one of the islet autoantibodies measured at the diagnosis of type 1 diabetes. The GADA results should therefore be accessible in all children and adolescents with newly diagnosed type 1 diabetes and thus be available for the assessment of future thyroid autoimmune disease. Although it may be too complex to include GADA and age at diabetes diagnosis in the standard screening algorithm, the physician might be extra observant for signs of hypothyroidism in young female patients positive for GADA at type 1 diabetes diagnosis.

Only 1.5% of the patients treated with thyroxine were positive for TGAb but not TPOAb at type 1 diabetes diagnosis. Another study found that TPOAb but not TGAb was related to elevated TSH in children with

type 1 diabetes (26). We therefore recommend only measurements of TPOAb in the screening to simplify and minimize cost.

In recent or ongoing severe illness, such as newly diagnosed type 1 diabetes, the hypothalamic-pituitary-thyroid axis may be abnormal without other signs of thyroid disease (27). Therefore, TSH levels at the clinical diagnosis of type 1 diabetes have not been considered of great value for assessing thyroid disease (9, 28), and it is often recommended that screening of thyroid function with TSH should not be done until glucose control has been established (29). In our study, TSH levels were taken at the actual diagnosis date, before established glucose control, and when patients still could be deranged because of critical illness. Therefore, we found it clinically relevant to investigate the predictive value of this initial TSH level for subsequent autoimmune hypothyroidism, although it is well known that thyroid function is directly linked to hypothyroid disease. When analyzing whether a patient already had autoimmune hypothyroidism at diagnosis, we chose a 90-day limit to enable reasonable time for clinical reevaluation of TSH levels after established glucose control. We found that TSH outside the reference limits at the time of diagnosis also predicted later thyroxine treatment in cases when treatment was not prescribed until years after diabetes diagnosis. We thereby assumed that TSH was normalized between diabetes debut until years later when thyroxine treatment was described, possibly indicating risk for later thyroid disease.

Because almost one-fourth of our patients were treated with thyroxine within 90 days of type 1 diabetes diagnosis (Fig. 2), it would be important to know when seroconversion to thyroid autoimmunity took place in relation to islet autoimmunity. Autoimmune hypothyroidism is seldom an acute diagnosis; reevaluation of thyroid function tests after stabilization of type 1 diabetes is common. We therefore estimated that children and adolescents prescribed thyroxine within 90 days of type 1 diabetes diagnosis were diagnosed with both diseases simultaneously because of screening for autoimmune thyroiditis at diabetes diagnosis. Hence, further studies of children at increased genetic risk for type 1 diabetes followed from birth, such as in The Environmental Determinants of Diabetes in the Young study (30), should prove of interest in determining the temporal appearance of TGAb, TPOAb, or both in relation to any of the islet autoantibodies.

Only 10 of 137 patients receiving thyroxine treatment were negative for thyroid autoantibodies and GADA and had a normal TSH at type 1 diagnosis. As reported, all of these patients were adolescents, and 5 of them received treatment more than 5 years after type 1 diabetes diagnosis, supporting that incidence of autoimmune thyroid disease increases with age and diabetes duration and that thyroid autoimmunity may develop after diabetes onset (19). Therefore, continuous screening for thyroid disease is needed in children and adolescents with diabetes, even if the initial samples at type 1 diabetes diagnosis prove negative for thyroid autoimmunity and GADA.

The median age for initiation of thyroxine treatment was 12.9 years (range, 3.6 to 25.7 years). This supports the current view that thyroid autoimmunity in type 1 diabetes is a phenomenon of late onset, with a peak around puberty (31, 32). We also confirmed that autoimmune thyroid disease is most common in girls. However, the girl to boy ratio of autoimmune thyroid disease in children and adolescents with type 1 diabetes was decreased compared with the general population (F to M, 2.7:1) (33), which indicates that the relative risk for a boy with type 1 diabetes to develop thyroid autoimmune disease is higher.

The strength of our study is that the large, nationwide cohort of almost all children diagnosed with type 1 diabetes could be identified in the Swedish National Board of Health and Welfare's Prescribed Drug Register for validation of data on thyroxine prescription. This approach to combine the Better Diabetes Diagnosis register with the Prescribed Drug Register is unique and enabled us to get information on treated thyroid disease in all patients. We are also gaining information on start time for thyroxine prescription, which makes it possible to exclude prescriptions due to congenital hypothyroidism. In addition, all patients had a confirmed diagnosis of type 1 diabetes supported by *HLA-DQ* genotypes and islet autoantibodies. We could thereby extend our previously reported negative association between genotypes containing *DQA1*01:01-B1*05:01* and thyroid autoantibodies to include autoimmune thyroid disease, although no clear, positive *HLA* correlations were found. Other immune regulatory genes outside the *HLA* loci and not studied here are thought to contribute to disease susceptibility both in autoimmune thyroid disease and type 1 diabetes, including the protein tyrosine phosphatase-22 gene and the cytotoxic T-lymphocyte–associated antigen-4 gene (34, 35). These genetic loci seem to be stronger for individuals with co-occurrence of AITD and type 1 diabetes (36).

A weakness of our study is the lack of information on development of thyroid autoimmunity before and between type 1 diabetes diagnosis and at the time when thyroxine was prescribed. It is therefore not possible to evaluate time from seroconversion to the diagnosis of autoimmune thyroid disease. There may also be local differences in the stage of disease at which thyroxine treatment is started. The standard of care in Sweden is to start thyroxine treatment in children with positive thyroid autoantibodies and repeatedly elevated TSH after performing ultrasonography of the thyroid gland. The

most common reason for thyroxine treatment is hypothyroidism due to autoimmune thyroiditis. A small number of children for whom thyroxine was given as a substitution in combination with thyreostatic agents due to hyperthyroidism may have been included, although the incidence of hyperthyroidism in children and adolescents in Sweden is as low as 1/100,000 patients per year in children <9 years old and 5/100,000 patients per year in those 10 to 19 years old (37). There might also be a few patients who received treatment after thyroidectomy or radiotherapy and/or chemotherapy.

None of the children in this cohort were prescribed thyroxine treatment during the neonatal period, excluding congenital hypothyroidism as a cause.

The current study provides strong observations that, taken together, would be useful for reaching a consensus on when and how to screen for autoimmune thyroid disease in children with newly diagnosed type 1 diabetes. In this large cohort of children and adolescents with type 1 diabetes, our analysis of islet and thyroid autoantibodies as well as TSH levels suggests that screening for autoimmune thyroid disease should be done at diabetes diagnosis with TPOAb and TSH. The most convenient and cost-effective method is then to screen with TSH annually in those who are TPOAb positive and every other year in those who are TPOAb negative at diabetes diagnosis. Abnormal TSH values at diabetes diagnosis should clearly be reevaluated. Clinicians may also take both age at diagnosis and GADA available at diagnosis into account when evaluating the risk of subsequent development of autoimmune hypothyroidism.

The following screening suggestions for autoimmune thyroid disease in children and adolescents with type 1 diabetes are based on markers at type 1 diabetes diagnosis:

- TPOAb negative at type 1 diabetes diagnosis with normal TSH: TSH measurement every other year
- TPOAb-positive with normal TSH and/or GADA-positive individuals <5 years old: TSH measurements every year

Appendix

The following are members of the Better Diabetes Diagnosis study group, all of whom are in Sweden. The location of the pediatric clinic for each member is given in parentheses: B.-O. Samuelsson (Borås), K. Snellman (Eskilstuna), A. Olivecrona (Falun), Å. Stenberg (Gällivare), L. Skogsberg (Gävle), B. Lindblad (Göteborg), G. Forsander (Göteborg), N. Nilsson (Halmstad), J. Neiderud (Helsingborg), T. Torbjörnsdotter (Huddinge), T. Hägg (Hudiksvall), K. Hemmingsson (Härnösand), K. Åkesson (Jönköping), G. Lundström (Kalmar), M. Ljungcrantz (Karlskrona), M. Forssberg (Karlstad), K. Larsson (Kristianstad), C. Gundewall (Kungsbacka), R. Enander (Linköping), U. Samuelsson (Linköping), A. Carlsson (Lund), H. Elding Larsson (Malmö), A. Brännström (Luleå), M. Nordwall (Norrköping), L. Hellenberg (Nyköping), E. Lundberg (Skellefteå), H. Tollig (Skövde), B. Björsell (Sollefteå), C. Marcus (Stockholm), E. Örtqvist (Stockholm/KS), I. Kockum (Stockholm), B. Stjernstedt (Sundsvall), N. Wramner (Trollhättan), R. Hanås (Uddevalla), I. Swenne (Uppsala), M. Blomgren (Visby), A. Thåström (Västervik), C.G. Arvidsson (Västerås), S. Edvardsson (Växjö), B. Jönsson (Ystad), T. Gadd (Ängelholm), J. Åman (Örebro), R. Florell (Örnsköldsvik), and A.-L. Fureman (Östersund).

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