Thyroid Autoimmunity in Children and Adolescents With Type 1 Diabetes

A multicenter survey

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OBJECTIVE — To investigate thyroid autoimmunity in a very large nationwide cohort of children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Data were analyzed from 17,749 patients with type 1 diabetes aged 0.1–20 years who were treated in 118 pediatric diabetes centers in Germany and Austria. Antibodies to thyroglobulin (anti-TG) and thyroperoxidase (anti-TPO) were measured and documented at least once in 7,097 patients. A total of 49.5% of these patients were boys, the mean age was 12.4 years (range 0.3–20.0 years), and the mean duration of diabetes was 4.5 years (range 0.0–19.5 years). A titer exceeding 100 units/ml or 1:100 was considered significantly elevated.

RESULTS — In 1,530 patients, thyroid antibody levels were elevated on at least one occasion, whereas 5,567 were antibody-negative during the observation period. Patients with thyroid antibodies were significantly older ($P < 0.001$), had a longer duration of diabetes ($P < 0.001$), and developed diabetes later in life ($P < 0.001$) than those without antibodies. A total of 63% of patients with positive antibodies were girls, compared with 45% of patients without antibodies ($P < 0.001$). The prevalence of significant thyroid antibody titers increased with increasing age; the highest prevalence was in the 15- to 20-year age group (anti-TPO: 16.9%, $P < 0.001$; anti-TG: 12.8%, $P < 0.001$). Thyroid-stimulating hormone (TSH) levels were higher in patients with thyroid autoimmunity (3.34 μU/ml, range 0.0–615.0 μU/ml) than in control subjects (1.84 μU/ml, range 0.0–149.0 μU/ml) ($P < 0.001$). Even higher TSH levels were observed in patients with both anti-TPO and anti-TG (4.55 μU/ml, range 0.0–197.0 μU/ml).

CONCLUSIONS — Thyroid autoimmunity seems to be particularly common in girls with diabetes during the second decade of life and may be associated with elevated TSH levels, indicating subclinical hypothyroidism.

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The prevalence of positive thyroid antibodies in children with type 1 diabetes varies considerably between 3 and 50% in different countries (1,2), and the clinical significance of these antibodies remains controversial. Moreover, there has been no consensus on screening for autoimmune thyroiditis in patients with type 1 diabetes.

The aim of this study was to investigate the prevalence of thyroid autoantibodies in a very large cohort of children and adolescents with type 1 diabetes from Germany and Austria, using data documented longitudinally in a computer-based program for the continuous documentation of treatment processes and outcomes (DPV-Wiss). In addition, the study addressed whether antibody positivity influences subclinical thyroid homeostasis, height and weight development, or glycemic control in young patients with diabetes.

RESEARCH DESIGN AND METHODS

— Data from children and adolescents with type 1 diabetes who were treated in 118 pediatric departments of university and general hospitals in Germany and Austria, including some specialized practices, were analyzed. These centers are members of the German Working Group for Pediatric Diabetology of the German Diabetes Association. For the purpose of quality management, all centers use a computer-based program for the continuous documentation of treatment processes and outcomes (DPV) in patients with diabetes (3). Participating centers transmit anonymous data from all their diabetic patients for central validation and analysis once every year. According to the guidelines of the German Diabetes Association, all centers are requested to document weight, height, BMI, blood pressure, findings on inspection of injection sites, and HbA_{1c} levels at least once every 6 months and cholesterol and triglyceride levels once every year. To date, there is no consensus for monitoring autoimmune thyroid disease in young patients with diabetes; however, most pediatric diabetologists in Germany routinely measure thyroid autoantibodies in children every 1–2 years. The longitudinal documentation of all DPV data comprises the DPV-Wiss database. From January

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Abbreviations: anti-TG, thyroglobulin antibodies; anti-TPO, thyroperoxidase antibodies; TSH, thyroid-stimulating hormone.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical and biochemical data in young patients with type 1 diabetes with or without positive thyroid antibodies (anti-TPO ≥100 units/ml or ≥1:100; anti-TG ≥100 units/ml or ≥1:100)*

	Patients with at least one positive thyroid antibody		Patients without positive thyroid antibodies	
	N	Mean ± SD or median (range)	*N*	Mean ± SD or median (range)
Age (years)	1,530	13.6 ± 3.8*	5,567	12.3 ± 4.3
Age at diagnosis (years)	1,530	8.4 ± 4.0*	5,567	7.8 ± 4.0
Duration of diabetes (years)	1,530	5.2 ± 3.9*	5,567	4.4 ± 3.9
Daily insulin dose (units/kg)	1,345	0.80 (0.0–2.6)	4,785	0.80 (0.0–4.3)
Height standard deviation score	1,530	−0.04 (−3.9 to 3.8)	5,567	−0.02 (−3.9 to 5.0)
BMI (kg/m^2)	1,530	19.9 (10.0–37.9)	5,567	18.9 (10.0–45.4)
HbA_{1c} (%)	1,511	8.1 (3.5–18.5)	5,492	8.2 (3.5–20.3)
TSH (μU/ml)	1,371	3.34 (0.0–615.0)*	5,115	1.84 (0.0–149.0)
TSH >3.5 μU/ml (%)	1,530	15.8*	5,567	7.8
Celiac disease (%)	1,530	0.85	5,567	0.63

Data correspond to the most recent data set with positive thyroid antibodies in the DPV-Wiss database. *$P < 0.001$ compared with patients without positive thyroid antibodies.

1985 to May 2001, data from 17,749 patients aged 0.1–20 years were included in this database.

Antibodies to thyroperoxidase (anti-TPO) and thyroglobulin (anti-TG) were measured and documented at least once in 7,097 children and adolescents. A total of 49.5% of these patients were boys, the mean age was 12.4 years (range 0.3–20.0 years), and the mean duration of diabetes was 4.5 years (range 0.0–19.5 years). Both antibodies were measured by commercially available radioimmunoassays in one laboratory by a semiquantitative agglutination assay. A titer exceeding 100 units/ml or 1:100 was considered significantly elevated. Thyroid-stimulating hormone (TSH) was measured by routine assays. TSH values >3.5 μU/ml were considered significantly elevated.

Growth and BMI data of patients were compared with an reference age-matched German population and expressed as standard deviation scores for chronological age (4,5).

Statistical analysis

Data were analyzed using the SAS statistical software package (SAS Institute, Cary, NC). Nonparametrical statistics (Wilcoxon's rank-sum test, Kruskal-Wallis test) were used for comparison among groups. Differences of frequencies for categorical variables were tested by the χ^2 test. Data are presented as mean ± SD for normal distributed variables or median (range) for non-Gaussian distributed parameters. Significant differences were assumed for $P < 0.05$.

RESULTS — Screening for thyroid antibodies was performed in 7,097 patients (39.9%) recorded in the DPV-Wiss database. A total of 1,530 patients (21.6%) were found to have significantly elevated titers of at least one thyroid antibody on at least one occasion, whereas 5,567 patients showed no significant elevation during the observation period. Clinical and biochemical characteristics of the study patients are summarized in Table 1. At the time of last entry in DPV-Wiss database, patients with thyroid antibodies were significantly older ($P < 0.001$) and had a longer duration of diabetes ($P < 0.001$) than those without antibodies. Furthermore, in these patients, diabetes had developed later in life ($P < 0.001$) (Table 1).

The prevalence of significant thyroid antibody titers increased with increasing age of patients and reached its maximum in the 15- to 20-year age group ($P < 0.001$, Fig. 1).

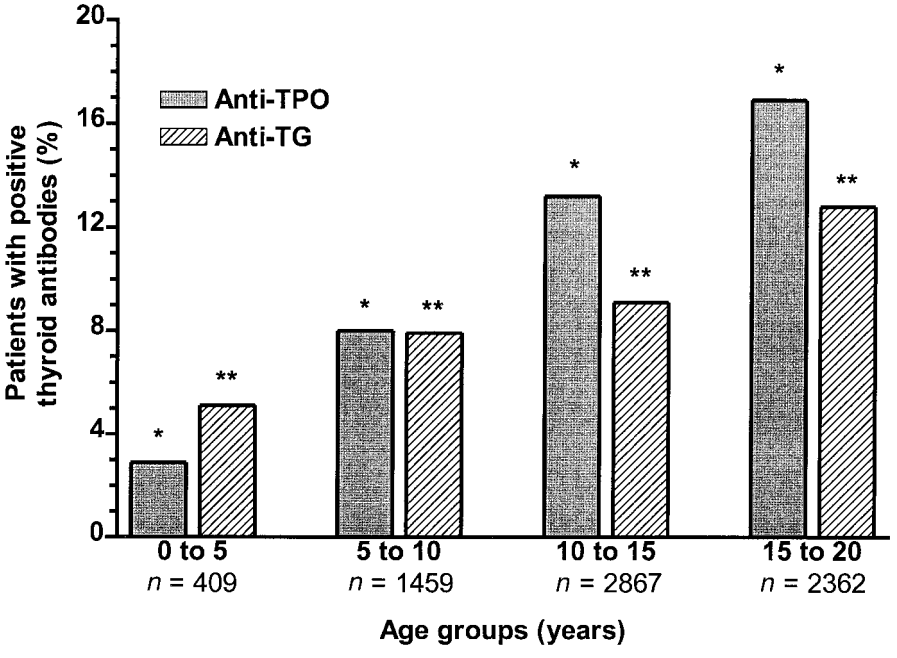

Figure 1—*Increasing prevalence of elevated thyroid antibodies (gray bars: anti-TPO; hatched bars: anti-TG) with increasing age of patients. The number of patients in every age group is depicted under the* x *axis.* * $P < 0.0001$, ** $P < 0.001$.

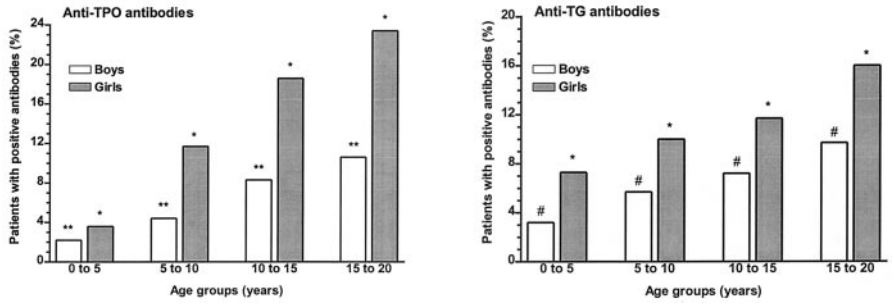

Figure 2—*Increasing prevalence of elevated thyroid antibodies (left panel: anti-TPO; right panel: anti-TG) stratified according to the sex and age of the patients.* * P < *0.0001,* ** P < *0.001,* # P = *0.006.*

In particular, thyroid autoimmunity was shown more commonly in girls: 63% of patients with positive antibodies were female compared with 45% in patients without antibodies ($P < 0.001$). This predominance was observed in all age groups until 20 years of age (Fig. 2).

TSH levels were significantly higher in patients with thyroid autoimmunity (3.34 μU/ml, range 0.0–615.0) compared with patients without antibodies (1.84 μU/ml, 0.0–149.0) ($P < 0.001$, Table 1). Even higher TSH levels were observed in patients with both anti-TPO and anti-TG (Fig. 3). Moreover, TSH levels differed according to the pattern of elevated thyroid antibodies: both anti-TPO and anti-TG positive, 4.55 μU/ml (0.0–197.0); only anti-TPO positive, 3.94 μU/ml (0.0–615.0); only anti-TG positive, 1.73 μU/ml (0.0–24.2); both negative, 1.87 μU/ml (0.0–292.0) ($P < 0.001$).

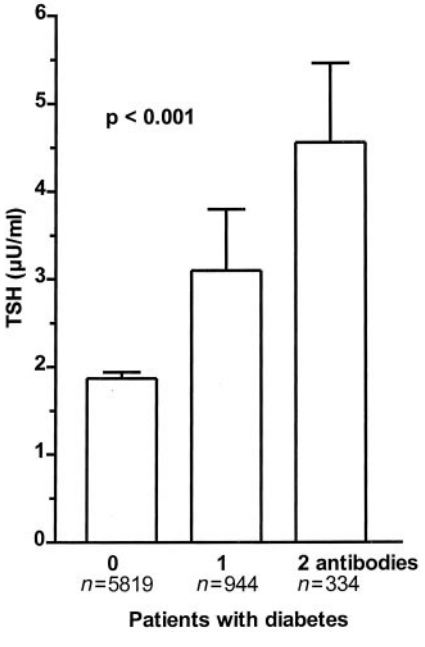

Figure 3—*TSH values according to the numbers of elevated thyroid antibody titers (>100 IU/ml or >1:100) in 7,097 children and adolescents with type 1 diabetes. Data are presented as mean + SEM.*

A total of 16% of patients with thyroid autoimmunity had abnormal TSH levels compared with 8% in the group without thyroid antibodies ($P < 0.001$, Table 1). In both groups, patients with elevated TSH levels were comparable regarding their gender (antibody-positive group, 35.2 vs. 36.5% male, $P = 0.7971$; antibody-negative group, 54.1 vs. 53.5% male, $P = 0.7086$) to those with normal TSH levels, but they were significantly younger at onset of diabetes (antibody-positive group, 7.7 ± 3.9 vs. 8.8 ± 3.9 years, $P < 0.001$; antibody-negative group, 7.2 ± 3.8 vs. 7.8 ± 4.0 years, $P = 0.001$).

Prescription for L-thyroxine was documented in 10.6% of patients with thyroid antibodies compared with 0.6% of those without antibodies. At the time of first entry of elevated thyroid antibodies, 5.8% of patients received L-thyroxine.

Glycemic control ($P = 0.132$) and daily insulin dose ($P = 0.487$) did not differ between patients with or without thyroid antibodies, respectively. Similarly, growth and weight development were comparable in both groups: 12.8% of patients with thyroid antibodies were overweight (BMI above 90th percentile) compared with 12.9% of those without antibodies.

The presence of celiac disease did not differ between patients with or without thyroid antibodies (0.85 vs. 0.63%).

CONCLUSIONS — These data support and extend previous findings from smaller cohorts documenting the high prevalence of thyroid autoimmunity in children and adolescents with type 1 diabetes in northern Europe (6,7). Because not all patients on the database were screened for autoimmune thyroiditis, one could speculate that this prevalence of 21.6% may be an underestimate. In Caucasian populations with diabetes in the U.S., a prevalence of 50% has been reported (2).

In this study, determination of thyroid antibodies was available in 40% of the total cohort. This may be due to the different diagnostic approaches among diabetologists participating in this study. Some of them measured antibodies after onset of puberty; others measured antibody levels only when suspicious symptoms appeared. Therefore, patients were only evaluated when thyroid antibodies had been determined at least once. In this subset, we found an increasing prevalence of thyroid antibodies with increasing age of the patients. In a recent study, Jaeger et al. (8) demonstrated significantly elevated thyroid antibody levels in adult patients with recent onset of type 1 diabetes. Also, in the general population without diabetes, the prevalence of positive test results for thyroid antibodies has been found to increase with age (9). As in previous studies (6,10), female subjects were significantly predisposed to thyroid autoimmunity at any age. Although it is unlikely that association between age or sex and antibody positivity may not exist in the total cohort, we cannot exclude this possibility, because the subset of patients studied was not randomly selected.

It is unknown whether these organ-specific antibodies are directly involved in the pathogenesis of the disease or whether they are just secondary to tissue destruction by thyroid-infiltrating T-cells (11). Furthermore, it is unclear whether anti-TPO antibodies are able to induce hypothyroidism by blocking the enzyme TPO (11). In a previous study, we found that patients with very high titers of anti-TPO as well as those with concomitant presence of anti-TPO and anti-TG are at high risk for abnormal TSH levels and/or ultrasound abnormalities such as diffuse hypoechogenicity and enlargement of thyroid gland (10). In the present study, patients with thyroid antibodies had significantly higher TSH levels than those

without thyroid antibodies, particularly when both anti-TPO and anti-TG were present. Furthermore, elevated anti-TPO antibodies seemed to be more specific for thyroid disorder than elevated anti-TG, because they were associated with higher TSH levels. This confirms recent findings by Padberg et al. (12). TSH elevations were also found in a group of patients without thyroid autoimmunity. This may be due to conditions other than autoimmunity, i.e., iodine deficiency resulting in thyroid dysfunction. In the past, in Germany, there were local differences concerning iodine disposability. However, intensive efforts have been made in recent years with improving results concerning the iodine supply (13).

In this database, only 10.5% of patients with thyroid autoimmunity received therapy with L-thyroxine. This may reflect the controversial discussion in the literature about the effectiveness of thyroid hormone treatment in euthyroid patients (normal T_4 and TSH concentrations) and in those with subclinical hypothyroidism (normal T_4 and elevated TSH concentrations) (12,14,15). Rother et al. (14) found that most children and adolescents with normal T_4 levels did not respond to thyroid hormone treatment with a reduction in goiter size, whether they had normal or elevated TSH levels. On the other hand, Padberg et al. (12) documented a significant reduction of both TSH and anti-TPO levels in euthyroid patients with autoimmune thyroiditis after 1 year of L-thyroxine treatment compared with those who were not treated. In a prospective study up to 12 years, Engler et al. (16) estimated the cumulative risk for overt hypothyroidism after 10 years to be 63% in patients with increased TSH and positive thyroid antibodies compared with only 22% in those with isolated elevation of TSH. Nevertheless, the clinical significance of autoimmune thyroiditis in children and adolescents with type 1 diabetes is still unclear. Chase et al. (17) reported reduced growth rates in children with diabetes and subclinical hypothyroidism, particularly in those with TSH values >50 mU/l. After treatment with L-thyroxine, growth velocity increased in prepubertal patients. In the present survey, growth data were not different between patients with or without thyroid antibodies. Furthermore, we found no difference concerning glycemic control in both groups. However, there is little information about the impact of subclinical thyroid abnormalities on the course of type 1 diabetes. In our opinion, there is still a great need for prospective intervention studies in this cohort.

Celiac disease is an autoimmune disorder associated with both type 1 diabetes (18) and autoimmune thyroiditis (19). However, diabetic patients with thyroid autoimmunity did not show a higher prevalence of celiac disease than those without significant thyroid antibodies. These data would support the hypothesis that the concomitant presence of diabetes with an additional autoimmune disorder, particularly autoimmune thyroiditis, is more common than the rare systemic autoimmune polyendocrinopathy disorder (APECED) associated with autosomal-recessive inheritance and gene mutations (20).

In conclusion, these data support the recommendation for regular, i.e., yearly, examinations of thyroid antibodies, particularly of anti-TPO, in all children and adolescents with type 1 diabetes commencing from onset of diabetes or, at latest, before puberty. In cases of antibody positivity, thyroid function tests and ultrasound assessment are recommended to minimize the risk of undiagnosed hypothyroidism in young patients with type 1 diabetes.

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