Hyperthyroidism in 276 Children and Adolescents with Type 1 Diabetes from Germany and Austria

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Key Words

Hyperthyroidism · Pediatric type 1 diabetes mellitus · DPV Initiative · Metabolic control · Microvascular disease

Abstract

Background/Aims: Little is known about the incidence and clinical consequences of hyperthyroidism in pediatric patients with type 1 diabetes mellitus (T1DM). **Methods:** We analyzed the DPV database (Diabetes Prospective Follow-Up Registry) to investigate the rate of hyperthyroidism in pediatric T1DM patients, its impact on metabolic control, and potential associations with organ-specific autoantibodies. **Results:** Hyperthyroidism was found in 276/60,456 patients (0.46%) and was associated with younger age, shorter diabetes duration, female sex, and reduced body mass index. Diabetic ketoacidosis (DKA) and hypoglycemia were more frequent in T1DM with comorbid hyperthyroidism, while long-term metabolic control (HbA1c) was similar in both groups. Absolute blood pressure and arterial hypertension rate were elevated in the hyperthyroid patients. Rates of microalbu-

minuria and diabetic retinopathy were not different. Thyroid-specific antibodies (thyroid peroxidase, thyroglobulin, thyroid receptor) were associated with hyperthyroidism. Thyroid volume and rates of cysts and nodules were higher, and echogenicity was decreased. **Conclusion:** Prevalence of hyperthyroidism is low in diabetic children with T1DM but increased compared to children <18 years without diabetes. Hyperthyroidism is primarily associated with acute diabetes complications (DKA and hypoglycemia) and affects blood pressure regulation. Long-term metabolic control or insulin requirement were not different.

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Introduction

Autoimmune diseases associated with type 1 diabetes mellitus (T1DM) are relatively common. In Germany and Austria, approximately 10% of pediatric patients with T1DM also have celiac disease (CD), and as many as

20% develop autoimmune thyroiditis (AIT) [1, 2]. Although most AIT patients present with Hashimoto's disease, a small number of patients are diagnosed with Graves' disease (GD). Generally, the lifetime prevalence of GD in Caucasian populations is estimated to be 0.5–1.0% [3, 4]. GD prevalence in Italian children with T1DM is 0.53%, and thus as high as in the general population [3]. In the Netherlands, T1DM appears to be more frequent in patients with GD than in the general population (1.7 vs. 0.22–0.26%) [5]. The combination of T1DM and GD may be part of type 2 or type 3 polyglandular autoimmune syndrome [6, 7].

In most cases, GD is diagnosed years after diabetes onset [3], but there are also reports of GD onset before or concurrently with the diagnosis of diabetes [8–10].

Severe hyperthyroidism appears to worsen glycemic control through different mechanisms: increase in intestinal glucose absorption, decrease in insulin secretion, decrease in the peripheral utilization of glucose due to insulin resistance, and increased gluconeogenesis [9, 7]. Thyrotoxicosis is also reported to trigger diabetic ketoacidosis (DKA). Thus, in the absence of other factors, thyrotoxicosis should be considered as a cause of DKA [10, 9]. On the other hand, DKA might mask the symptoms of hyperthyroidism and GD [4].

Most of these data result from single observations or small cohorts. The only investigation based on a large cohort of pediatric patients focused on the influence of T1DM on the clinical course of GD rather than the influence of hyperthyroidism on metabolic control in diabetes [3].

Our objectives, therefore, were to study (1) the frequency of hyperthyroidism in children and adolescents with T1DM, (2) the influence of hyperthyroidism on metabolic control and on the frequency of acute complications in diabetic children and adolescents, and (3) the possible associations with organ-specific autoantibodies that are common in T1DM.

Patients and Methods

DPV (Diabetes Prospective Follow-Up Registry) is an electronic documentation system for patients with diabetes that is widely used in Austria and Germany. Based on this continuous diabetes data acquisition program for prospective surveillance, a prospective multicenter survey was designed. Initiated in 1995, the DPV data documentation collects demographic, anthropometric, and diabetes-related characteristics of patients with diabetes, and is used as a quality control system [1].

The data are generated locally in an electronic health record and transmitted in anonymous form to the University of Ulm, Germany, for central evaluation and analysis every 6 months. In-

consistent data are reported back to the participating centers for confirmation or correction and are then re-entered into the cumulative database.

Study Population

As of September 2013, 60,456 patients with T1DM aged <20 years and younger than 18 years at diabetes onset from 405 centers were documented in the DPV database. The patients were grouped according to their insulin regime: conventional therapy (CT) with 1–3 insulin injection time points per day, intensive CT (ICT) with 4 or more injections per day, and insulin pumps.

A diagnosis of hyperthyroidism was based on the International Classification of Diseases codes supplied by the local treatment centers, use of thyreostatic medication, or documented laboratory results from the most recent treatment year. In the case of multiple consultations, data were aggregated during the most recent year.

Hypertension was assumed if (1) the documented blood pressure levels were above the 95th percentile of the reference cohort of 'The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents' [11], (2) a diagnosis of hypertension was stated by the treating physician, or (3) if antihypertensive medication was prescribed.

Dyslipidemia was defined as the presence of abnormal lipid levels (cholesterol >200 mg/dl, HDL <35 mg/dl, LDL >130 mg/dl, and/or triglycerides >150 mg/dl), a diagnosis of dyslipidemia by the treatment center, or the use of lipid-lowering drugs.

Glycated hemoglobin (HbA1c) levels were determined locally at each participating center and standardized to the Diabetes Control and Complication Trial (DCCT) reference range of 4.05–6.05% [12]. Body mass index (BMI) data were evaluated as standard deviation (SD) scores (SDS values, or z-scores) based on a cohort of 34,422 healthy German children (17,147 boys and 17,275 girls) [13]. Thyroid volume was determined by ultrasound at the local centers; the volumes were compared using SD scores with a cohort of healthy German children from Berlin [14].

Most pediatric diabetes centers in Germany and Austria screen for markers of T1DM-associated autoimmune diseases on a regular basis. Antibodies specific for CD (such as transglutaminase, endomysium, or gliadin autoantibodies), autoantibodies against β -cell epitopes (islet cell antibodies, insulin, glutamate decarboxylase, and tyrosine kinase autoantibodies), and autoantibodies against parietal cells of the stomach and adrenal cortex.

Statistical Analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, N.C., USA). Descriptive results are shown as mean $\pm$ SD or as percentage. Differences between patients with and without hyperthyroidism were analyzed using the Wilcoxon signed rank test or the χ^2 test, as appropriate.

Multivariable regression models were calculated with PROC GLIMMIX using linear regression for continuous parameters with estimation technique-restricted maximum likelihood. Logistic regression was used for dichotomous parameters, and Poisson regression for event rates. Adjustment for age, sex, and diabetes duration was used to correct for differences in these parameters between patients with and without hyperthyroidism.

Based on observed marginal frequencies, adjusted estimates (means $\pm$ SD or percentages) were calculated. Values of $p < 0.05$ and $p < 0.01$ were considered significant and highly significant, respectively.

Table 1. Demographic and clinical characteristics of the study population as a whole and by thyroid state

Parameter	Total	Hyperthyroid	Euthyroid	p
<i>Demography</i>				
Patients, n (%)	60,456 (100)	276 (0.46)	60,180 (99.54)	
Age, years	14.35±4.23	12.27±4.09	14.36±4.22	<0.0001
Sex, % male	52.6	34.1	52.7	<0.0001
Height, cm	159.6±20.8	151.9±21.2	159.7±20.8	<0.0001
Height SDS	−0.07±1.1	0.18±1.1	−0.07±1.1	0.0003
Weight, kg	56.9±20.1	48.8±19.1	57.0±20.1	<0.0001
Weight SDS	0.43±1.5	0.43±0.9	0.43±1.5	0.99
BMI	21.45±4.2	20.05±4.1	21.46±4.2	<0.0001
BMI SDS	0.53±1.0	0.41±1.0	0.53±1.0	0.037
<i>Clinical diabetes</i>				
Age at diagnosis, years	8.55±4.3	8.22±4.2	8.55±4.3	0.234
Diabetes duration, years	5.81±4.3	4.07±4.2	5.81±4.3	<0.0001
CT, %	10.1	16.9	10.1	0.0002
ICT, %	61.3	58.5	61.3	0.33
CSII, %	28.6	24.6	28.6	0.15
Insulin dose, IU/kg/day	0.95±0.4	0.92±0.4	0.95±0.4	0.27
Injections per day	5.8±2.3	5.4±2.3	5.8±2.3	0.001
β-Blocker use, %	0.15	3.99	0.14	<0.0001

Significant differences are marked in bold. CSII = Continuous subcutaneous insulin infusion (insulin pump).

Results

Characteristics of the Study Population

Table 1 summarizes the demographic and clinical characteristics of our cohort. The mean age of the children included in this investigation was 14.4 years, mean diabetes duration 5.8 years, mean BMI SDS 0.53, and the required average insulin dosage $0.95 \text{ units} \times \text{kg body weight}^{-1} \times \text{day}^{-1}$. 61% of the children were on ICT, 29% on pump therapy, and 10% on conventional insulin treatment.

With an average HbA1c of 8.3%, metabolic control was suboptimal according to targets recommended by the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association (ADA). There were 7.9 episodes of DKA, 17.5 episodes of severe hypoglycemia (requiring assistance or treatment for coma/convulsion), and 4.2 episodes of hypoglycemic coma per 100 patient-years. 40% of the patients had dyslipidemia, 32% arterial hypertension, 15% microalbuminuria, 1% macroalbuminuria, and 2% retinopathy (table 2).

Hyperthyroid Patients

Demographics

Hyperthyroidism during the most recent year of treatment was diagnosed in 276 (0.46%) out of all 60,456 pa-

tients. Patients who were positive for hyperthyroidism were younger and more often female, had a shorter duration of diabetes, and lower body weight and BMI. Absolute height was lower compared to euthyroid patients, but height SDS was increased (table 1).

Metabolic Control

Metabolic control as represented by the HbA1c level was similar in both groups after adjustment for age, sex, and diabetes duration: 8.44% (68.8 mmol/mol) in the hyperthyroid children versus 8.32% (67.7 mmol/mol) in the euthyroid children, $p = 0.34$, linear regression (table 2). Insulin requirement was slightly but not significantly lower in the hyperthyroid patients (table 2), and the hyperthyroid patients received conventional insulin therapy significantly more often (table 1).

The Poisson regression model (adjusted for age, sex, and diabetes duration) showed the hyperthyroid patients to be at a 2.3-fold increased risk for DKA: 18.1 episodes of DKA per 100 patient-years (hyperthyroid patients) versus 7.7 episodes per 100 patient-years (euthyroid patients), $p < 0.001$ (table 2).

Similarly, hypoglycemia was more frequent in the hyperthyroid compared with the euthyroid patients: severe hypoglycemia 34.4 versus 17.2 episodes per 100 patient-

Table 2. Metabolic parameters

Parameter	Hyperthyroid	Euthyroid	p
Patients, n (%)	276 (0.46)	60,180 (99.54)	
HbA1c, %	8.4	8.3	0.34
Insulin, IU/kg/day	0.98	0.95	0.21
DKA, episodes/100 patient-years	18.1	7.7	<0.0001
Severe hypoglycemia, episodes/100 patient-years	34.4	17.2	<0.0001
Hypoglycemic coma, episodes/100 patient-years	8.1	4.0	0.026
Cholesterol, mg/dl	165.5	180.5	<0.0001
Arterial hypertension, %	43.7	31.1	<0.0001
Microalbuminuria, %	14.3	14.2	0.97
Retinopathy, %	0.95	1.1	0.90

Age-, sex-, and diabetes duration-adjusted parameters of metabolic control, blood pressure regulation, and the rate of diabetic complications depending on thyroid state. Note the higher rates of DKA and of hypoglycemia in hyperthyroid patients. Significant differences are marked in bold.

years ($p < 0.0001$), hypoglycemia with coma 8.1 versus 4.0 episodes per 100 patient-years ($p = 0.026$), all by Poisson regression (table 2).

The hyperthyroid patients used β -blockers 28.5 times more often than the nonhyperthyroid patients (3.99 vs. 0.14%; table 1). The highest use of β -blockers was seen in the group of hyperthyroid patients with severe hypoglycemia (6.8%), followed by hyperthyroid patients without severe hypoglycemia (3.5%). The use of β -blockers by the euthyroid patients was negligible (with hypoglycemia 0.03%, without hypoglycemia 0.08%).

After correcting for age, sex, and diabetes duration, cholesterol levels were significantly lower in the hyperthyroid patients (165.5 vs. 180.5 mg/dl, $p < 0.0001$; table 2). Arterial blood pressure and the rate of hypertension were increased in the hyperthyroid group and remained so after adjustment [43.7 vs. 31.1%, odds ratio (OR) 1.7, $p = 0.0001$; table 2].

Thyroid Function Tests, Ultrasound

Thyroid-stimulating hormone (TSH) levels were significantly lower in the hyperthyroid group, as expected. The sonographic features also showed significant differences between the two groups: larger absolute thyroid volume and volume SDS, and a higher rate of cysts and nodules in the gland were associated with hyperthyroidism, whereas echogenicity was more often decreased (table 3).

Typical clinical symptoms of hyperthyroidism were rare in our patient cohort: diarrhea, sweating, sleep disturbances, and other clinical symptoms of hyperthyroidism were each recorded in 3 patients and weight loss in 4 patients.

Autoimmunity

Thyroid autoimmunity was more frequent in the hyperthyroid compared to the euthyroid patients: 73.7 versus 18.2% were positive for any thyroid autoantibody, and 23.3 versus 6.2% were positive for TSH receptor antibodies (TR-Ab; $p < 0.0001$, Wilcoxon test). After adjustment for age, sex, and diabetes duration, these differences persisted: thyroid peroxidase antibodies (72.5 vs. 15.3%, OR 14.6, $p < 0.0001$), thyroglobulin antibodies (54.1 vs. 12.2%, OR 8.4, $p < 0.0001$), TR-Ab (25.8 vs. 6.1%, OR 5.4, $p < 0.0001$), and any thyroid antibody (78.7 vs. 17.0%, OR 18.1, $p < 0.0001$; table 4).

There was only a slight tendency towards a higher frequency of the nonthyroid autoantibodies (i.e. antibodies against β -cells, adrenal cortex, and parietal cells, and for CD) in the hyperthyroid group; however, these differences were not statistically significant (table 4).

Discussion

Of the 60,456 T1DM patients under 20 years of age investigated in this study, 276 were diagnosed with hyperthyroidism during the most recent year of therapy. The prevalence of 0.46% was thus approximately 140 times higher than in children under 18 years of age from Southern Germany (3.25/100,000, 0.00325%) [15].

Several studies have reported a higher lifetime prevalence of hyperthyroidism in adult diabetic patients with T1DM: approximately 1.2% of individuals with T1DM in the US [16] and 0.5% of patients in Scotland were found to be hyperthyroid [17], whereas in Sicily (Italy) 14 out of

Table 3. Thyroid parameters

Parameter	Hyperthyroid	Euthyroid	p
Patients, n (%)	276 (0.46)	60,180 (99.54)	
TSH, μ U/ml	1.1	2.2	<0.0001
Thyroid volume, ml	17.1	9.1	0.0006
Thyroid volume-SDS	8.0	3.1	0.0029
Cysts, %	28.5	13.4	0.037
Nodules, %	23.8	6.4	0.004
Decreased echogenicity, %	18.9	77.6	<0.0001

Age-, sex-, and diabetes duration-adjusted thyroid parameters depending on thyroid status. Note the higher frequency of sonographic signs of AIT in the hyperthyroid patients. Significant differences are marked in bold.

Table 4. Organ-specific autoantibodies

Parameter	Hyperthyroid	Euthyroid	p
Patients, n (%)	276 (0.46)	60,180 (99.54)	
TPO-Ab, %	72.5	15.3	<0.0001
Tg-Ab, %	54.1	12.2	<0.0001
TR-Ab, %	25.8	6.1	<0.0001
All thyroid Ab, %	77.1	16.1	<0.0001
β -Cell Ab, %	87.6	85.3	0.47
CD-specific Ab, %	20.0	16.3	0.18
Adrenal cortex Ab, %	9.8	9.3	0.93
Parietal cell Ab, %	17.8	13.9	0.71

Age-, sex-, and diabetes duration-adjusted frequencies of autoantibodies associated with thyroid disease and/or type 1 diabetes by thyroid status. Significant differences are marked in bold. TPO-Ab = Thyroid peroxidase antibodies; Tg-Ab = thyroglobulin antibodies; Ab = (auto)antibodies.

470 (3%) patients with T1DM were diagnosed with GD, all before the onset of diabetes [8].

In children and adolescents with T1DM, the lifetime prevalence of hyperthyroidism appears to be quite low: 0.2% in Turkey [18], 0.53% in Italy [3], and 0.7% in Poland [7]. Only in the Madrid area (Spain) were T1DM children found to be subclinically hyperthyroid in 3% and overtly hyperthyroid in 6% of cases [19]. Thus, although we aggregated the rate of hyperthyroidism from the most recent documented year as a point prevalence, our data appear to be in line with most European studies. Hyperthyroidism can thus be considered relatively rare in children with T1DM, particularly when compared with the high rate of Hashimoto's disease. However, we cannot exclude the possibility that hyperthyroidism might be underreported in our patient cohort.

Clinical signs and symptoms were reported in only 4 of the 276 patients with hyperthyroidism. Accordingly,

average TSH and lipid levels were lower in the hyperthyroid group but still clearly within the normal range. T1DM children are under continuous medical surveillance, and the parents assumingly pay more attention to the health status of their children. Therefore, it could be speculated that other diabetes-related diseases are earlier recognized in the T1DM patients. In the hyperthyroid patients, ultrasonography showed the typical features of hyperthyroidism, including increased thyroid volume, a higher rate of cysts and nodules, and decreased echogenicity.

Hyperthyroidism in our pediatric cohort appears to have been rather subclinical than overt. Patients with overt, clinically relevant hyperthyroidism lose weight, and in children growth is stimulated. In our cohort, hyperthyroidism was only subclinical or transient, and therefore the influence of the insulin therapy predominated and stimulated weight gain, resulting in similar

weight SDS in both groups. Height SDS was increased in the hyperthyroid children, and metabolic control was similar in the hyperthyroid and the euthyroid patients. So, the higher thyroid hormone levels in the hyperthyroid children might have stimulated growth.

High L-thyroxine levels have been reported to enhance glucose uptake, hepatic gluconeogenesis, and insulin resistance and to increase lipase activity, resulting in higher lipolysis and eventually contributing to DKA or chronic hyperglycemia [10].

Long-term metabolic control, expressed as HbA1c levels, was not impaired in the hyperthyroid patients, which is in contrast to earlier reports in the literature [4, 9]. It is therefore not surprising that the rates of albuminuria and diabetic retinopathy did not differ between the hyperthyroid and the nonhyperthyroid group, possibly due to the short diabetes duration and the comparatively good metabolic situation in the hyperthyroid patients.

In contrast, DKA is approximately 3.5 times more frequent in our hyperthyroid patients. Long-term metabolic control (HbA1c levels) was similar in the hyperthyroid and the euthyroid patients. So, we think the significant differences between the two groups in terms of DKA cannot be explained by metabolic control expressed as HbA1c. From our data, we conclude that other factors are relevant, such as the different thyroid state. Hence, hyperthyroidism should be considered a potential cause for 'unexplainable' episodes of DKA.

On the other hand, these metabolic pathways should protect from hypoglycemia and not enhance them. The higher rate of clinically relevant hypoglycemia in the hyperthyroid patients may be attributable to the 28.5-fold higher use of β -receptor blocking medication. In our study, β -blocker use was highest in the hyperthyroid patients with severe hypoglycemia. As β -blockers are known to mask symptoms of the early sympathetic response to hyperglycemia, patients experience no catecholamine actions and enter straight into the neuroglycopenic phase of hypoglycemia without warning symptoms. Secondly, metabolic control will improve as hyperthyroidism is treated or remits spontaneously. Due to the high initial insulin demand in the hyperthyroid state, insulin doses might not be reduced sufficiently and might contribute to the increased rate of hypoglycemia as the metabolic situation improves. It is conceivable that in our cohort both pathways may have contributed to the high association between hypoglycemia and hyperthyroidism.

Thyroid antibodies are more frequent in the hyperthyroid patients, as expected. A rate of approximately 20% positivity for thyroid antibodies has previously been re-

ported for T1DM children in Germany and Austria [2], this rate being slightly higher than in other European countries (Poland 10%, Turkey 12%) [7, 18].

Only 23% of the patients with hyperthyroidism in our cohort were positive for thyroid receptor antibodies. It remains speculative whether the other patients had the hyperthyroid form of Hashimoto's disease or whether they actually had GD and had meanwhile returned to a negative TR-Ab status. Remission of GD occurs in approximately 40–60% of adult patients, but children with GD appear to reach remission less often (15–30%) [20]. Only 33% of Italian children with GD remitted after 2 years of antithyroid medication. Positive outcome was related to lower initial TR-Ab levels, faster normalization of TR-Ab, lower initial thyroid volume, and lower blood pressure [21]. The hyperthyroid patients in our study presented with higher thyroid volume, higher blood pressure, and a higher rate of increased TR-Ab, all of these factors being negative predictors of remission in GD. Hence, it is unlikely for most hyperthyroid patients in our study population that they had GD previously and turned TR-Ab negative again. In fact, it is quite likely that most patients had never been TR-Ab positive and therefore present with the hyperthyroid manifestation of Hashimoto's thyroiditis.

In our cohort, hyperthyroidism was associated with only a slightly increased rate of CD antibodies. By contrast, CD prevalence in British patients with GD showed a 20-fold increase compared to the general UK population (0.9 vs. 0.047%) [22]. In Dutch patients with AIT, the prevalence of CD appears to be fairly low, both for Hashimoto's disease and GD, with Hashimoto's thyroiditis being associated with T1DM significantly more often [23]. The rate of other nonthyroid autoantibodies, i.e. antibodies against adrenal cortex and parietal cells, showed no association with hyperthyroidism in our patient population. Hence, hyperthyroidism does not appear to be an important risk factor for other autoimmune diseases except CD in children with T1DM.

Conclusion

Hyperthyroidism in children and adolescents with T1DM is rare but significantly more frequent than in children under 18 years without diabetes from Southern Germany.

In most pediatric hyperthyroid T1DM patients, hyperthyroidism tends to be subclinical, showing no or only few clinical signs or symptoms; while it may well have an

impact on acute complications of T1DM, such as DKA or hypoglycemia, it has only little influence on long-term metabolic control. In our opinion, general screening of diabetic children for hyperthyroidism using TR-Ab is not necessary. However, careful clinical monitoring for signs and symptoms of hyperthyroidism and TSH testing should be performed, and if unexplained metabolic deterioration occurs, hyperthyroidism should be considered after other factors have been excluded.

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