

Thyroid diseases – ally or enemy of type 1 diabetes in children and adolescents? Choroby tarczycy – wróg czy przyjaciel cukrzycy typu 1 u dzieci i młodzieży?

Natalia Ogarek, Anna Mrówka, Przemysław Jarosz-Chobot

Department of Pediatrics and Children's Diabetology, Medical University of Silesia, Katowice, Poland

Abstract

Introduction: Autoimmune thyroid diseases (AIT) are one of the most common disorders associated with type 1 diabetes (T1D) and they are capable of influencing its course. For Hashimoto's lymphocytic thyroiditis, the incidence is 14–28%, while for Graves-Basedow hyperthyroidism it is 0.5–7%.

Aim of the study: Assessment of type 1 diabetes in the pediatric population with coexisting autoimmune thyroid diseases: Hashimoto's lymphocytic thyroiditis and Graves-Basedow's disease.

Material and methods: Analyzing publications from the PubMed scientific database from 1990 to May 2020.

Results: Among pediatric patients with T1D and coexisting thyroid autoimmunity insufficient glycemic control is usually observed. Reported average increase in glycated hemoglobin concentration ranges from 7.9 to 9.2%.

In children with T1D and subclinical hypothyroidism, an increased number of episodes of hypoglycemia was noted – 5 vs. 2 episodes per year among children with euthyroidism. In hyperthyroidism patients the number of episodes of hypoglycemia was 34.4 vs. 17.2 per 100 incidents in euthyroidism patients. An increased occurrence of diabetic ketoacidosis events may also be observed – 18.1 vs. 7.7 per 100 patients with euthyroidism per year. The risk of developing chronic complications in the form of cardiovascular diseases is also higher. However, basing on the available literature, this subject is still debatable.

Conclusions: Autoimmune thyroid diseases often accompany and interfere with type 1 diabetes in children and adolescents. Paying special attention to the different course of diabetes in the presence of thyroid disorders is an important and essential element of diabetes care.

Key words:

metabolic disorders, children and adolescents, type 1 diabetes, autoimmune thyroid disease.

Streszczenie

Wprowadzenie: Autoimmunologiczne choroby tarczycy są jedną z najczęstszych jednostek chorobowych towarzyszących cukrzycy typu 1 i mogą wpływać na jej przebieg. Dla limfocytarnego zapalenia tarczycy typu Hashimoto częstość ta wynosi 14–28%, natomiast dla nadczynności tarczycy typu Gravesa-Basedowa 0,5–7%.

Cel pracy: Przedstawienie przebiegu cukrzycy typu 1 w populacji pediatrycznej ze współistniejącymi autoimmunologicznymi chorobami tarczycy: limfocytarnym zapaleniem tarczycy typu Hashimoto oraz chorobą Gravesa-Basedowa.

Materiał i metody: Bazę danych stanowiły artykuły naukowe z PubMed z lat 1990–2020.

Wyniki: U dzieci i młodzieży ze współistniejącą autoimmunizacją tarczycy obserwuje się zwykle niedostateczną kontrolę glikemii. Opisywany średni wzrost stężenia hemoglobiny glikowanej, w zależności od publikacji waha się od 7,9 do 9,2%.

U dzieci z subkliniczną niedoczynnością tarczycy obserwowano zwiększoną liczbę epizodów hipoglikemii – 5 vs 2 epizody na rok wśród dzieci z eutyreozą. Natomiast w nadczynności tarczycy liczba epizodów hipoglikemii wynosiła 34,4 vs 17,2 epizodów na 100 pacjentów z eutyreozą. W nadczynności tarczycy obserwuje się również zwiększoną częstość występowania epizodów cukrzycowej kwasicy ketonowej – 18,1 vs 7,7 na 100 pacjentów z eutyreozą na rok. Wyższe jest także ryzyko rozwinięcia odległych powikłań w postaci chorób sercowo-naczyniowych. Niemniej jednak w dostępnej literaturze istnieją rozbieżne doniesienia na ten temat.

Wnioski: Autoimmunologiczne choroby tarczycy często zaburzają jej przebieg i terapię. Zwrócenie szczególnej uwagi na odmienną przebiegu cukrzycy przy współwystępowaniu schorzeń tarczycy jest ważnym i podstawowym elementem opieki diabetologicznej.

Słowa kluczowe:

dzieci i młodzież, zaburzenia metaboliczne, cukrzyca typu 1, autoimmunologiczna choroba tarczycy.

Introduction

Type 1 diabetes (T1D) is one of the most common chronic diseases in childhood. According to World Health Organization (WHO) incidence rate of T1D ranges from 0.5 to over 60 cases annually per 100 000 children aged under 15 years [1]. In Poland, in 2018, National Health Fund estimated that there are approximately 22 000 children with diabetes under 18 years old [2]. Among children with T1D, the coexistence of other autoimmune disorders is often observed. Type 1 diabetes etiopathogenesis allows to understand its frequent occurrence with other autoimmune diseases. Most studies that tried to explain its genetic background and molecular mechanism focus on the MHC locus encoding HLA proteins in humans. They are one of the most important genes that underlies coexistence of thyroid autoimmunity (AIT) and T1D. In patients with T1D, the presence of haplotypes HLA-DRB1*0404, -DQB1*0301, -DPB1*0201 is strongly associated with positive anti-TPO, while the primary susceptibility allele in Graves disease is HLA-DRB1*03 [3, 4].

Other major genes associated with risk for T1D and AIT are: cytotoxic T-lymphocyte-associated antigen-4, *PTPN22* gene that encodes the lymphoid tyrosine phosphatase protein and FOXP3. All these susceptibility genes may underlie the coexistence of T1D and AIT [5].

There are numerous reports regarding coincidence of T1D and other autoimmune disorders such as thyroid disease, celiac disease, adrenal insufficiency, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis, autoimmune hepatitis, autoimmune gastritis, hypogonadism, pernicious anemia, vitiligo, scleroderma. Occasionally, some components of these diseases may appear sequentially, making them qualified as autoimmune polyglandular syndrome (APS). Type 1 diabetes occurs in APS type 2 and 3. Type 2, also known as Schmidt's syndrome, in addition to T1D, is characterized by Addison's disease, thyroid autoimmunity and others. Type 3 includes thyroid autoimmunity and pernicious anemia, vitiligo, alopecia areata, celiac disease, hypogonadism and more [6, 7]. It is a common knowledge that in patients with T1D, including children and adolescents, coexistence of thyroid disease is the most popular one out of the whole family of autoimmune disorders. It is estimated to be 2–4 times higher than in the general population. For Hashimoto's thyroiditis, the prevalence is 14–28%, while Graves' hyperthyroidism is found in 0.5–7% of children with T1D [8]. This observation in the case of AIT is confirmed by other authors who report a prevalence of 15.5% AIT among children with T1D with a significant prevalence in girls than in boys (21.9 vs. 9.3%) [9]. Numerous studies have been conducted on the presence of anti-thyroid antibodies: anti-thyroid peroxidase and anti-thyroglobulin in children with T1D. The frequency of their occurrence is significantly higher than in the general population. Depending on the study, from 2 up to 12.3% of patients develop autoimmune thyroid disorder in the form of Hashimoto disease. In the citations mentioned above the diagnosis of AIT was based on the same criteria - it depended on the serum concentration of total TSH and positive thyroid antibodies: anti-TPO, anti-TG [8, 10].

Furthermore, one of the latest FinnDiane follow-up studies (Finnish Diabetic Nephropathy Study) analyzed an extensive group of 4,758 patients with T1D and 12 710 patients without T1D, with a large age range of the study group (mean age 51.4 years). It was identifying autoimmune diseases through national register of medical data in the years 1970–2015 and found that the risk of hypothyroidism increases by 1.7% as the age of T1D diagnosis increases. There was no significant relationship between the age of patients and the risk of developing hyperthyroidism [11]. There are conflicting and limited data analyzing the course and metabolic control of T1D during preadolescence and adolescence in the presence of thyroid disease. Currently available database does not contain any comprehensive studies combining previous reports on the impact of thyroid diseases on the course of T1D in children and adolescents. This fact prompted the authors to attempt to summarize the available literature in this field.

Aim of the study

Assessment of the influence of autoimmune thyroid disease on T1D course in children and adolescents.

Material and methods

The aim of the study was accomplished by analyzing publications from the PubMed scientific database from 1990 to May 2020. The following keywords were used: type 1 diabetes, hypoglycemia, hyperglycemia, diabetic ketoacidosis, glycated hemoglobin, complications, height, BMI, dyslipidemia, insulin demand, anti-thyroid antibodies, anti-thyroglobulin antibodies (anti-TG), anti-thyroid peroxidase antibodies (anti-TPO), anti-TSH antibodies (TRAb), hyperthyreosis, Graves' disease, autoimmune thyroid diseases, comorbidities with T1D, children, adolescents. 35 scientific reports were selected for the study.

Prevalence of anti-thyroid antibodies in children and adolescents with type 1 diabetes

An Australian meta-analysis involving nearly 3,000 children and adolescents and 800 adults reported that 25% children with T1D had positive thyroid autoantibodies. It was also noted that they appeared most often during puberty (over 12 years of age or after 9 years of illness), with a predominance in females [12, 13]. However, in a publication from the Charité Children's Hospital in Berlin in a prospective study of 659 children, both the children with an average duration of diabetes of 1.2 (0–14.8) years and those with newly diagnosed diabetes had positive anti-TPO in 15.4% of cases and anti-TG in 14.4% of them, with a predominance in girls. In a subgroup of 126 children with newly diagnosed T1D, 18% had positive anti-TPO and anti-TG

antibodies. In addition, 9.4% (62) of patients were diagnosed with AIT based on TSH concentration and thyroid ultrasound image. During a ten-year follow-up, almost half of children with positive antibody results developed lymphocytic thyroiditis, with the peak incidence at 12 years [14].

Polish researchers based on retrospective observation carried out in 2000-2004 found anti-TG and anti-TPO antibodies in 27 out of 222 (12.16%) Silesian children with newly diagnosed T1D. Average age at diagnosis in this group was 9.92 ± 4.50 (0.50–17.92). A significant difference was observed in the age of children with a positive test result. Same as in the Charite Children's Hospital publication, they were older (11.67 ± 3.92) compared to children with negative antibody results (9.67 ± 4.58). There was no significant difference in sex [15], unlike other studies that report a higher frequency of thyroid antibodies in girls [14].

This result was lower than in the research of other Polish authors. Korpala-Szczyrska with her group estimated on a slightly smaller group (119 subjects) the presence of anti-thyroid anti-TPO and anti-TG antibodies in 32% of children (from 2 up to 16 years of age) with newly diagnosed T1D [16].

An additional interesting issue is the search for a correlation between the presence of antibodies associated with the destruction of β cells and antibodies characteristic of AIT. Observation of the pediatric population in Libya has shown a link between the occurrence of anti-glutamic acid decarboxylase (anti-GAD) antibodies and production of anti-thyroid (anti-TG and anti-TPO) antibodies. In the group of 218 children, 16.2% had positive anti-GAD/anti-IA-2 antibodies (anti-tyrosine phosphatase antibodies) and anti-TPO/anti-TG [17].

This is also confirmed by observations carried out on adult patients. T1D patients with positive anti-GAD antibodies were significantly more likely to have anti-TPO and anti-TG antibodies [18]. Moreover, described correlation between ZnT8 and the occurrence of AIT can be found. There is an interesting Swedish study from 2018 based on nearly 2000 10-years old without overt T1D but with increased risk for T1D, including HLA risk. Some of the antibodies were measured: anti-TPO, anti-Tg, GADA, IA-2A and ZnT8AR/W/QA. Anti-TPO was positively associated with GADA, IA-2A and ZnT8AR/W/QA, while anti-TG was positively associated only with ZnT8R/W/QA. Interestingly, a strong correlation between anti-TPO, anti-TG and ZnT8AR/W/QA was found only in boys. However, although males positive for GADA and IA-2A were positive for thyroid autoantibodies, ZnT8R/W/QA positive males showed no correlation to the thyroid autoantibodies. Contrary, in females, no correlation was found between thyroid autoantibodies and any of the islet autoantibodies. The authors suggest that thyroid autoimmunity in boys may depend on a concurrent autoimmune condition, such as T1D or islet autoimmunity. Furthermore, high levels of islet autoantibodies may increase risk of AIT. However, in girls, AIT is independent of any islet autoantibodies [19]. The association between thyroid autoantibodies and ZnT8R/W/QA was also found in another study. This analysis of individual variants of ZnT8A showed significant association between anti-TPO and ZnT8RA. Furthermore, newly diagnosed children with T1D and positive ZnT8A have an increased risk of developing AIT [20].

Assessment of T1D metabolic control based on HbA_{1c} glycosylated hemoglobin

Glycated hemoglobin (HbA_{1c}) is the gold standard for assessing long-term metabolic control of diabetes and the risk of vascular complications. This indicator depends not only on the level of glucose in the last 3 months but, among others, on the turnover of red blood cells as well [21]. According to the recommendations of the Diabetes Poland which are being published yearly since 2005, HbA_{1c} optimal value for children, adolescents and young adults should be equal to or less than 6.5% (48 mmol/l) in order to reduce cardiovascular risk [22].

Most studies of Hashimoto's lymphocytic thyroiditis in the hypothyroidism phase and its effect on HbA_{1c} indicate a tendency for reaching higher values compared to children and adolescents with T1D and normal thyroid hormone function. A good example of this behavior is the 16-year (2001–2016) prospective observation of a group of over 250 children up to 18 years of age with T1D where 16% of them were diagnosed with hypothyroidism. Diagnosis was based on elevated TSH level, normal fT4 values and a positive test for anti-TPO antibodies and / or with ultrasound markers of thyroiditis. HbA_{1c} values in children with AIT were significantly higher: 9.2 ± 1.5 vs. $7.9 \pm 0.7\%$ without AIT [13].

Moreover, a four-year (2008–2012) multicenter Polish study confirmed insufficient glycemic control among children with T1D and its coexistence with AIT. Observation included 330 children with T1D and AIT as well as 309 children with T1D without thyroid immunization markers. Mean age of the children from study and control group was 13 years and the mean duration of diabetes was 5 and 6 years, respectively. The HbA_{1c} value was significantly higher in children with comorbidity of T1D and AIT and was equal to 7.9 (6.90 – 9.10%) [18]. Contrary to the above results, Italian authors, in a retrospective assessment of 280 children including 4.6% diagnosed with AIT, did not observe a significant effect of hypothyroidism on HbA_{1c} levels in children with T1D. Metabolic control parameters, including glycosylated hemoglobin, were analyzed for 2 years every 3 months before and after the diagnosis of hypothyroidism [23].

Hypoglycemia

According to the Diabetes Poland 2020, hypoglycemia is diagnosed in people with diabetes when their blood glucose falls below 70 mg/dl (3.9 mmol/l), regardless of clinical symptoms. Hypoglycemia is defined as a clinically significant if glucose level drops to 54 mg/dl (3.0 mmol/l) or lower. Symptoms of hypoglycemia may also occur at higher glucose levels, even > 100 mg/dl (5.6 mmol/l), in the event of its rapid decrease [22]. The thyroid hormones, among others, intensify gluconeogenesis and glycogenolysis, therefore in hypothyroidism we can expect an increased frequency of hypoglycemia episodes [24]. On the other hand, in hyperthyroidism, due to high glucose concentration, a patient with T1D usually uses high doses of insulin in an attempt to control their glycemia which often causes

high glycemia variability and sometimes results in induction of iatrogenically hypoglycemia. In the cited articles both hyperthyroidism and hypothyroidism in the course of autoimmune thyroid disorders can lead to episodes of hypoglycemia. Previously mentioned study of Italian authors indicates that children with T1D and subclinical hypothyroidism are associated with an increased risk of symptomatic hypoglycemia. Patients with subclinical hypothyroidism had significantly more ($p < 0.05$) symptomatic hypoglycemic episodes within 12 months of diagnosis of hypothyroidism. After diagnosing subclinical hypothyroidism based on the clinical picture of patients 5 severe incidents of hypoglycemia in this group were noted compared to 2 episodes in the control group. However, thyroid hormone replacement therapy led to an equalization of blood glucose levels and, as a result, a significant reduction in the number of hypoglycemic episodes [23].

The above reports are confirmed by the Chase *et al.* research team which observed an increase in the number of hypoglycemia occurrences in children with T1D and coexisting hypothyroidism [25].

Furthermore, in hyperthyroidism (Graves' disease and the hyperthyroidism phase in the course of Hashimoto's disease) the number of hypoglycemia episodes was higher than in children with T1D but without AIT. One of the examples may come from DPV (Diabetes Prospective Follow-Up Registry) multicenter study involving over 60 000 patients with T1D under 20 years of age, including 276 with hyperthyroidism. Diagnosis of hyperthyroidism was based on the codes of the International Classification of Diseases provided by local treatment centers, usage of thyrostatic drugs or documented laboratory results from last year of treatment. Analysis of this extensive material confirmed a significantly higher incidence of episodes of severe hypoglycemia which are defined as requiring the assistance or treatment of coma/convulsions among people with hyperthyroidism. The number of severe incidents per year was 34.4 per 100 patients with hyperthyroidism vs. 17.2 episodes per 100 patients with euthyroidism ($p < 0.0001$) [26].

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is an acute dangerous complication of T1D. As a result of insulin deficiency and an increase in counter regulatory hormones, hyperglycemia, ketosis and metabolic acidosis occur [27]. An interesting issue comes with observation of thyroid hormone behavior in patients in whom T1D disclosure has been associated with DKA ($pH < 7.3$). This relationship was analyzed in several publications. For example, thyroid function analysis in 16 children aged 4.5–6 years with T1D and DKA before and after insulin treatment showed no significant difference between thyrotropin levels and triiodothyronine uptake [28]. However, a relationship between fT_3 , T_3 and blood pH levels during DKA was observed. The following conclusion was made: the lower the pH, the lower the hormone level [29]. This relation was also found in a retrospective study conducted by Yan-Yan Hu [30].

DKA is a common acute complication in children and adolescents with T1D and hyperthyroidism in the course of Graves' disease and in the hyperthyroidism phase of the Hashimoto's disease [7].

The above-quoted DPV report mentioned a significantly higher incidence of DKA in children and adolescents with T1D and hyperthyroidism compared to patients with diabetes and euthyroidism. The number of DKA episodes in children and adolescents with T1D and hyperthyroidism was 18.1 compared to 7.7 occurrences/100 patients per year with euthyroidism ($p < 0.001$) [26].

A particularly interesting and worth quoting study is the case report of the simultaneous occurrence of thyroid crisis and DKA, although it concerns a 37-year old patient. The clinical picture displays atypical DKA complicated by thyroid crisis which made diagnosis much more difficult. In the end, the patient was diagnosed with Graves' disease and T1D [31].

Dyslipidemia

Thyroid hormones stimulate synthesis, degradation and mobilization of lipids as well as biliary excretion of cholesterol [24]. Therefore, hypothyroidism, if not treated effectively, can lead to dyslipidemia [12]. Increased total cholesterol, LDL fraction and atherogenic factors were found which furthermore increase the risk of cardiovascular complications in young patients with T1D. Analysis of the DPV registry database (22 747 patients below 25 years old, mean age: 13.7 ± 4.25 with duration of T1D: 5.72 ± 3.92 years) showed in 7.2% of cases with subclinical hypothyroidism significantly higher total cholesterol (178.7 vs. 175.3 mg/dl) and LDL cholesterol (97.0 vs. 93.7 mg/dl) in comparison with euthyroid patients [32].

A Polish multicenter study also found a significant reduction in HDL cholesterol (3.68 mg/dl) and an increase in triglyceride level (7.16 mg/dl) in the study group [18].

It is worth noting that people with hyperthyroidism have higher risk of cardiovascular events due to the gradually joining hypertension [32].

Growth disorders

Based on the pathophysiology, due to the action of thyroid hormones and the delay in skeletal age, one can expect linear growth abnormalities and abnormal bone accrual (density and quality). Furthermore, hypothyroidism is associated with a decrease in the secretion of GH and glucocorticoids in vivo studies in humans examining [24]. However, there are contradicting reports regarding the effect of autoimmune subclinical hypothyroidism on growth disorders.

Both Greek and German authors tackled the evaluation of this subject in their multicenter studies. A prospective study of Greek authors included: 144 children and adolescents with T1D at the age of 12.3 ± 4.6 with duration of diabetes 4.6 ± 3.8 years [33]. The German-Austrian multicenter study collected

results from 118 pediatric departments, based on which they analyzed data of 17 749 patients under 20 years old with an average duration of diabetes of 4.5 (0–19.5) years. In the studies mentioned above, no difference in growth was found between T1D patients with and without subclinical hypothyroidism [33, 34]. The lack of influence is also confirmed by Italian researchers in their publications [23].

In contrast, the study published 20 years earlier, from the 90's, presents a different view. Subclinical hypothyroidism was assessed on the basis of TSH and thyromegaly found in thyroid ultrasound. Children had a reduced growth rate, especially if TSH levels exceeded 10 μ IU/l, while thyroid hormone replacement therapy only led to improved growth in prepubescent patients. In addition, children with subclinical hypothyroidism and T1D had worse glycemic control than children with T1D but without subclinical hypothyroidism [25]. However, less advanced therapeutic options were available back then. Furthermore, relatively small group of children with T1D and subclinical hypothyroidism was diagnosed in the first place.

Daily insulin demand

Daily insulin requirement in children with T1D, including those with AIT, is an important element in the process of equalization and control of patient diabetes.

In previously mentioned multicenter study based on the DPV registry, no difference in long-term metabolic control and insulin requirements was found [26]. Likewise, in another report there was no distinction in daily insulin requirement. A twelve-year study from the Rijeka University Hospital in Croatia discussed nearly 150 under 21 years old patients with T1D. 15.5% of them were diagnosed with AIT. The time from the develop-

ment of T1D to AIT was 3.3 ± 2.5 years [9]. The same conclusions were made in Mohn *et al.* study [23].

However, there are also different reports which do not confirm previous observations. For example, Korzeniowska in a four-year multicenter study noted that children with AIT and T1D have significantly lower insulin requirements than in the control group (-0.15 , range -0.20 to -0.11 U/kg body weight per day). Observation covered over 600 children, over half of them had T1D coexisting with AIT [18].

Summary

AIT often accompany and interfere with T1D in children and adolescents. Thyroid dysfunction in children with T1D may impact negatively many different areas of metabolic control, for example by an increase in HbA_{1c} levels or more frequent episodes of hypoglycemia. In addition, AIT can worsen total cholesterol, LDL and triglyceride levels which impacts progress of cardiovascular diseases. Due to the high risk of thyroid diseases occurring in patients with T1D, the recommendation of systematic monitoring for thyroid diseases and their treatment were included in national and international guidelines of diabetes care for children, adolescents and young adults [22, 35]. As recommended by the Diabetes Poland 2020 following laboratory tests should be performed at the onset of the disease: anti-TPO and anti-TG antibodies, TSH, free T4. In case of positive thyroid antibodies or thyroid dysfunction, the thyroid ultrasonography should be performed, followed by TSH, anti-TPO and anti-TG every 2 years (at the discretion of the treating physician) [22]. Paying special attention to the different course of diabetes in the presence of thyroid disorders is an important and essential element of pediatric diabetes care.

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