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Status of antithyroid immunity in children and adolescents with type 1 diabetes mellitus

Natalia Shliakhova[1], Svitlana Chumak[2]

[1]Kharkiv State Academy of Physical Culture, Kharkiv, Ukraine
[2]SI «Institute for Children and Adolescents Health Care of the NAMS of Ukraine», Kharkiv, Ukraine

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Corresponding author:
Natalia Shliakhova
Kharkiv State Academy of Physical Culture, Kharkiv, Ukraine
orcid.org/0000-0003-2126-2184
e-mail: nv_shlyakhova@ukr.net

Svitlana Chumak
orcid.org/0000-0002-6532-3797

Abstract

Purpose: to determine the frequency of increased antibodies to thyroperoxidase in children and adolescents with type 1 diabetes, and to determine possible risk factors such as age, gender, age of manifestation, duration and level of glycemic control of type 1 diabetes for the development of autoimmune thyroid dysfunction.

Material & Methods: anti-thyroid peroxidase antibodies (anti-TPO) level was determined in 165 children aged 8-18 years (85 girls and 80 boys) with T1DM, considering gender, duration of type 1 diabetes Mellitus (T1DM), level of sexual development at the time of T1DM manifestation and at the time of examination.

Results: increased anti-TPO levels were observed in 15.8% of children with T1DM. In girls, antibodies were found twice as often (p=0.04) and were detected at a much younger age (p=0.007). The frequency of AB pressure levels before TPO significantly increased in puberty compared to childhood and puberty (p=0.03). Presumably, increased anti-TPO levels were found in children who developed T1DM before the onset of puberty (p=0.004).

Conclusions: the obtained data indicate that increased levels of antithyroid antibodies are associated with female sex, puberty age and manifestation of T1DM before the onset of puberty. This confirms the need to screen all children and adolescents with type 1 diabetes for thyroid antibodies and antigens, which will reduce the risk of developing autoimmune-induced thyroid dysfunction.

Key words: thyroid autoantibodies, children, diabetes.

Анотація

Наталія Шляхова, Світлана Чумак. Стан антитиреоїдного імунітету у дітей та підлітків, що хворіють на цукровий діабет 1 типу. Мета: визначити частоту підвищених антитіл до тиропероксидази у дітей та підлітків, що хворіють на цукровий діабет 1 типу(ЦД1), та визначити можливі фактори ризику, такі як вік, стать, вік маніфестації, тривалість та рівень глікемічного контролю цукрового діабету 1 типу на розвиток аутоімунної дисфункції щитовидної залози. **Матеріал і методи:** рівень АТ до ТПО було визначено у 165 дітей 8-18 років (85 дівчат і 80 хлопців), хворих на ЦД1 з урахуванням статі, тривалості цукрового діабету 1 типу, рівня статевого розвитку на момент маніфестації ЦД1 та на момент обстеження. **Результати:** підвищені рівні АТ до ТПО спостерігалися у 15,8% дітей, хворих на ЦД1. У

дівчат антитіла зустрічалися вдвічі частіше (p=0,04) та виявлялись в значно молодшому віці (p=0,007). Частота підвищених рівнів АТ до ТПО суттєво збільшувалася в пубертаті порівняно з дитячим та пубертатним віком (p=0,03). Вірогідно частіше підвищені рівні АТ до ТПО виявлялися у дітей, які захворіли на ЦД1 до початку статевого дозрівання (p=0,004). **Висновки**: отримані дані свідчать, що підвищенні рівні антитиреоїдних антитіл асоціюються з жіночою статтю, пубертатним віком та маніфестацією ЦД1 до початку статевого дозрівання. Це підтверджує необхідність скринінгу всіх дітей та підлітків із цукровим діабетом 1 типу на антитіла та антигенів щитовидної залози, що дозволить знизити ризик розвитку аутоімунно-індукованої тиреоїдної дисфункції.

Ключові слова: тиреоїдні аутоантитіла, діти, цукровий діабет.

Introduction

Type 1 diabetes mellitus (T1DM) appears as a result of autoimmune destruction of β-cells, which usually turns to absolute insulin deficiency. This disorder in clinical practice is closely related to autoimmune-induced thyroid dysfunction (AITD), since these endocrine diseases are linked by the same pathophysiological mechanism, and some genetic factors may contribute to the co-occurrence of autoimmune disease of both the thyroid gland and T1DM (Husebye, Anderson & Kämpe, 2018). Most current research focus on MHC-II proteins as the most important genes for the combination of T1DM and AITD. Thus, in patients with T1DM, the presence of haplotypes HLA-DRB1*0404, HLA-DQB1*0301, HLA-DPB1*0201 is strongly associated with increased levels of antibodies to thyroperoxidase (anti-TPO), while the primary allele of susceptibility to Graves' disease is HLA- DRB1*03 (Huber, Menconi, Corathers, Jacobson, & Tomer, 2008; Kahles, Fain, Baker, Eisenbarth, & Badenhoop, 2015). Cytotoxic T-lymphocyte-associated antigen-4 is considered to be another major gene associated with the risk of developing T1DM and AITD; the PTPN22 gene, which encodes the lymphoid tyrosine phosphatase protein, and FOXP3. All these susceptibility genes may be the basis of the coexistence of T1DM and AITD (Tomer, & Menconi, 2009).

Available data indicate a combination of type 1 diabetes not only with AITD, but with other autoimmune diseases such as rheumatoid arthritis, psoriasis, vitiligo, hypogonadism, systemic lupus erythematosus and others, which may not only coincide with diabetes 1, but also be components of the autoimmune polyglandular syndrome (Ragusa et al., 2019; Krzewska, & Ben-Skowronek, 2016). Meanwhile, the combination of T1DM and AITD is most common not only in adults, but also in children and adolescents. According to available estimates, AITD in patients with T1DM is 2-4 times higher than population indicators. Shun, Donaghue, Phelan, Twigg, & Craig (2014) showed that the risk of thyroid dysfunction was higher in individuals with evidence of autoimmune thyroid disease and was higher in children compared to adults.

According to available data, autoimmune thyroid diseases occur in 17-30% of both children and adults with T1DM, and these patients have an increased risk of autoimmune-induced hypothyroidism (Hashimoto's thyroiditis), as well as hyperthyroidism (Graves' disease) (Husebye et al., 2018; Shun. et al., 2014; Jin et al.,2011). It has been shown that patients with T1DM develop thyroid dysfunction at an earlier age compared to the population, and its onset is associated with more aggressive manifestations of AITD and poorly controlled T1DM in children (Fatourechi, Ardakani, Sayarifard, & Sheikh, 2017).

Most research indicate that autoimmune hypothyroidism is present in 14–28% of children with T1DM, while Graves' hyperthyroidism is present in 0.5–7% (Fatourechi, Ardakani, Sayarifard, & Sheikh, 2017; Ridha, & Al Zubaidi, 2019; Severinski, Banac, Severinski, Ahel, & Cvijović, 2009). It should be noted that the frequency of AITD depended on gender (Shun, C. B. et al., 2014; Severinski et al., 2009; Orzan, Novac, Mihu, Tirgoviste, & Balgradean, 2016) and was significantly higher in girls than in boys (21.9% versus 9.3%) (Severinski et al., 2009). According to the results of the HUNT research, adult women with T1DM also have approximately twice the risk of developing hypothyroidism, whereas men with T1DM have approximately four times the risk of developing hypothyroidism (Fleiner, Bjøro, Midthjell, Grill, & Åsvold, 2016; Umpierrez et al., 2003; Kordonouri et al., 2002).

Numerous studies concern the presence of antithyroid antibodies – antibodies to thyroid peroxidase and thyroglobulin in patients with T1DM, regardless of age. The frequency of their detection is much higher than in the general population and ranges from 2 to 12% (Ridha, & Al Zubaidi, 2019; Fleineret al., 2016; Umpierrez et al., 2003; Kordonouri et al., 2002; Triolo et al., 2011). Umpierrez et al. (2003)in a prospective 18-years research showed that patients with T1DM and positive anti-TPO have an almost 18-fold higher risk of developing hypothyroidism compared to patients with T1DM and normal antibody levels [14]. The Finnish Diabetic Nephropathy Study FinnDiane analyzed a group of 4758 patients with T1DM and 12710 patients without T1DM with a large age range (mean age 51.4 years) and found that the risk of hypothyroidism increased by 1.7% as the duration of T1DM increased (Kordonouri et al., 2002; Mäkimattila, Harjutsalo, Forsblom, Groop, & FinnDi-

ane Study Group, 2020). Meanwhile, a reliable relationship between the age of patients and the risk of developing hyperthyroidism was not found. In addition, it is noted that the onset of thyroid dysfunction is often associated with the duration of diabetes (Kordonouri et al., 2002; Kakleas et al., 2021).

It should be noted that there are still conflicting and limited data on the course and control of T1DM in childhood and adolescence in the presence of thyroid dysfunction.

The aim of this study was to determine the frequency of increased antibodies to thyroperoxidase in children and adolescents with type 1 diabetes, and to determine possible risk factors such as age, gender, age of manifestation, duration and level of glycemic control of type 1 diabetes for the development of autoimmune thyroid dysfunction.

Material and methods of research

Participants

165 children (85 girls (51.5%) and 80 boys (48.5%) from 8 to 18 years of age, suffering from type 1 diabetes and who were in the endocrinology department of the SI «ICAH NAMSU» were involved in the research. Criterion inclusion in the research was the duration of DM1 for more than one year (from 1 to 16 years).

Research was conducted in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, and the current legislation of Ukraine. The research protocol was approved by the medical ethics committee at the SI «Institute for Children and Adolescents Health Care of the NAMS of Ukraine». Parents and patients provided written informed consent to participate in the research.

Research design

The analysis of anti-TPO was carried out considering gender, level of sexual development at the time of examination and diagnosis of T1DM, duration of T1DM and level of glycemic control.

Research participants were divided into groups depending on:

- the level of sexual development (T1-T4) at the time of the research, which was evaluated according to the Marshal W.A. scale. and Tanner J.M. (Marshall, & Tanner, 1969; Marshall, & Tanner, 1970);

- level of sexual development (T0-T3) at the time of diagnosis of T1DM;

- the duration of the course of T1DM (<5 years, from 5 to 10 years, >10 years);

- levels of glycemic control (optimal (HbA1c< 7.5%), suboptimal (7.5%≤HbA1c≤9.0%), with high risk (HbA1c>9.0%)) in accordance with the recommendations of ISPAD 2018 (DiMeglio et al., 2018).

Serum analysis

Quantitative determination of antibodies to thyroid peroxidase in blood serum was carried out by enzyme-linked immunosorbent assay (ELISA). A level of antibodies <33 U/ml was considered normal.

Statistical analysis

Statistical analysis of the obtained data was carried out using the SPSS 26.0 statistical program package. We calculated a minimum sample size of 163 children to detect a frequency of 12% and assuming a margin of error of 5% (95% CI, 7-17%). The frequency of the presence of anti-TPO of different levels was calculated as the proportion with values above the normal value. Chi-square tests and Fisher's exact test were used to detect any significant changes in categorical variables between groups. Data are presented with odds ratio estimates with 95% confidence intervals (OR; (95% CI)). The number of observations (n), mean ± standard deviation (mean (SD) and frequency (%) were used to summarize the nominal variables. Comparisons of data between groups were performed using one-way analysis of variance (ANOVA). The level of significance was set at $p<0.05$.

Results of the study

The average age of the research participants was mean (SD) 14.1 (2.8) years, the duration of diabetes 1 – 6.6 (3.7) years, the age of manifestation of T1DM – 7.7 (3.6) years, the level of

Table 1. General characteristics of children with type 1 diabetes depending on gender

Parameters	Boys, n=80	Girls, n=85
Age (years), mean (SD)	14,2 (2,8)	14,0 (2,8)
IMT (kg/m^2), mean (SD)	19,5 (2,3)	20,4 (2,9)
Diabetes manifestation (years), mean (SD)	7,5 (3,5)	7,8 (3,5)
Diabetes duration (years), mean (SD)	7,0 (3,8)	6,3 (3,7)
HbAc1, mean (SD)	8,8 (2,0)	8,9 (2,3)

HbAc1 – 8.9 (2.2)% without significant differences by sex (Table 1).

The assessment of the level of puberty at the time of the examination made it possible to establish that the majority of the research participants corresponded to actual or late puberty (30.9% and 33.9%, respectively) (Fig. 1 A)

By the level of glycemic control, there were also no significant differences (Fig. 1 B). Optimal control was observed in 28.5% of children, suboptimal – in 30.3%, glycemic control with high risk – in 41.2% of children without significant differences in frequency between boys and girls.

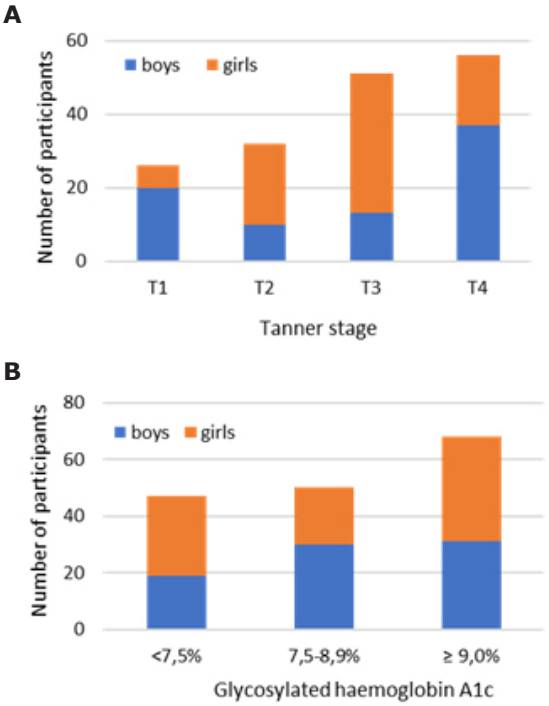

Fig. 1. Distribution of patients with type 1 diabetes mellitus according to the Tannner stage (**A**) and HbA1c (**B**)

Among children with T1DM, the largest number were patients with a disease duration of 5 to 10 years (44.2%), regardless of gender (45.0% of boys and 43.5% of girls). More than a third of patients had a disease duration of up to 5 years (34.5%) and 21.2% of children were ill for more than 10 years, also without a significant difference by sex (Fig. 2A).

In most children, T1DM was diagnosed in childhood (56.4%, OR=2.2; (95% CI 1.1-4.8), p=0.03) or in prepubertal age (24.1%). It should be noted that the manifestation of T1DM in prepubescent age occurred more often in girls than in boys (31.8% vs. 17.5%). During the pubertal period, the diagnosis of T1DM was established much less often without significant differences by sex (Fig. 2B).

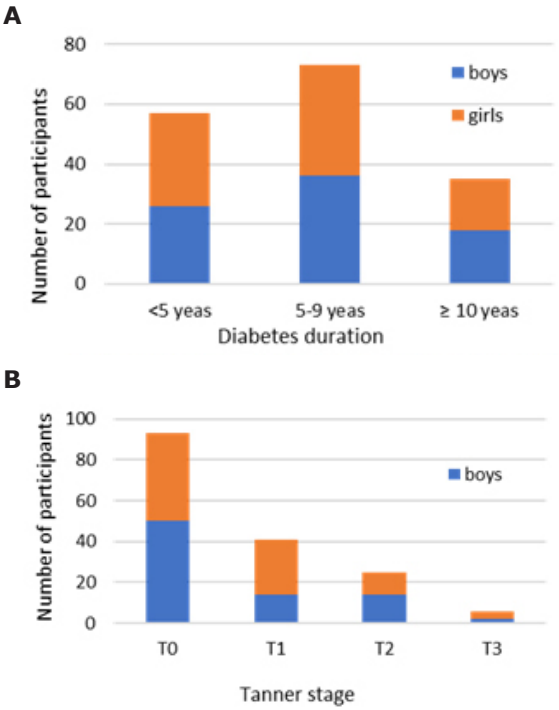

Fig. 2. Distribution of patients with type 1 diabetes mellitus according to the duration of the disease (**A**) and Tanner stage`s (**B**)

An increased anti-TPO was detected in 26 children and adolescents (15.8%), patients with T1DM. In terms of age, body mass index, disease duration, and HbA1c level, patients with normal and increased anti-TPO probably did not differ (table 2).

The obtained data indicate that the frequency of increased Anti-TPO significantly depended on sex (Fig. 3A). In girls, antibodies were found twice as often (21.2%) than in boys (10.0%),

Table 2. General characteristics of children depending on the presence of anti-TPO

Parameters	Normal ≤ 30 U/ml 139	Increased >30 U/ml 26	p-Value
Age (years), mean (SD)	14,2 (2,9)	13,9 (2,5)	0,5
Sex: boys, n (%) girls, n (%)	72 (51,8) 67 (48,2)	8 (30,8) 18 (69,2)	0,04
IMT (kg/m²), mean (SD)	19,9 (2,6)	20,2 (2,9)	0,5
Diabetes manifestation (years), mean (SD)	8,0 (3,5)	6,1 (3,2)	0,01
Diabetes duration (years), mean (SD)	6,5 (3,7)	7,4 (4,1)	0,3
HbA1c, mean (SD)	9,0 (2,2)	8,1 (2,0)	0,07

(OR=2.4; (95% CI 1.0-5.9), p=0.04). In addition, girls had high Anti-TPO at a much younger age – 12.9±2.3 years, than boys (15.7±2.0 years, p=0.007).

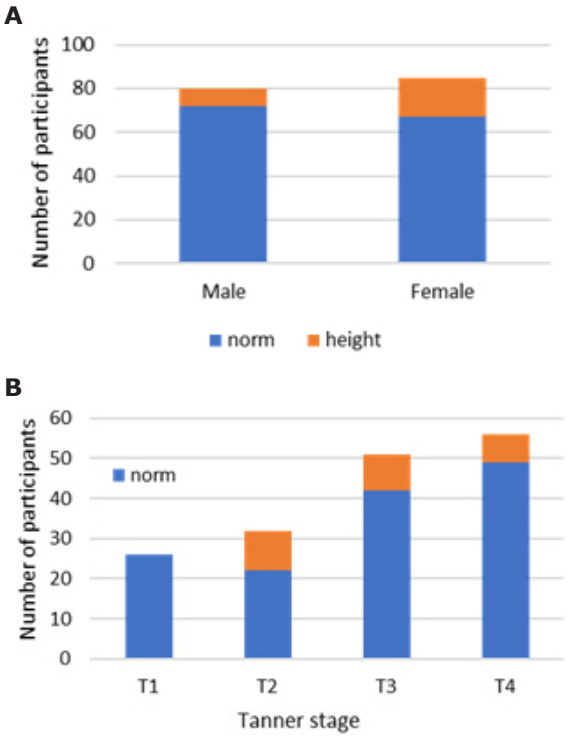

Fig. 3. Anti-TPO prevalence estimates in serum for sex (A) and Tanner stage (B)

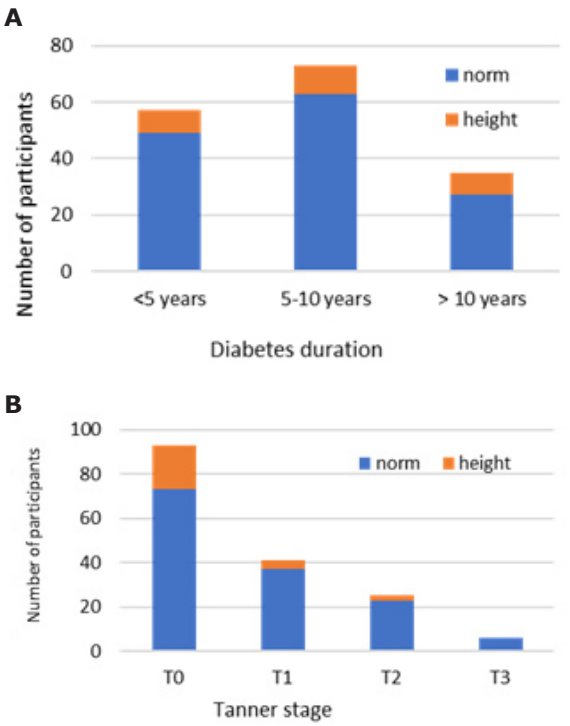

Fig. 4. Anti-TPO prevalence estimates in serum for diabetes duration (**A**) and Tanner stage`s manifestation (**B**)

At the same time, despite the absence of probable differences by age, the obtained results indicate that increased Anti-TPO were not determined in prepubertal children (Fig. 3B). During the period of puberty, the number of children with increased anti-TPO significantly increases, and already at puberty itself (T3 and T4 stages according to Tanner), the frequency of increased anti-TPO is likely to be higher than in children of prepubertal age (OR= 2.4; 95% CI [1.0-5.9], p=0.03).

Our research did not show a reliable relationship between the duration of T1DM and the presence of anti-TPO (Fig. 4A). It should be noted that anti-TPO was detected twice as often in children with a disease duration of more than 5 years (10.9%) compared to 4.9% of children whose disease history did not exceed 5 years (4.9%).

In addition, the age of diagnosis of T1DM in patients with an increased level of anti-TPO was probably younger (6.1±3.2 years) than in the group with a normal level of anti-TPO (8.0±3.5 years, p=0,01). It means that anti-TPO was significantly more often detected in children who developed T1DM at an earlier age (table 2). It is interesting that in girls with increased anti-TPO, the manifestation of T1DM was determined at a much younger age – at 5.0±2.6 years versus 8.6±2.9 years in boys (p=0.004).

Thus, most often the increased level of anti-TPO was found in children who began to suffer from T1DM in childhood. This allows us to assume that patients with T1DM, in whom the manifestation of diabetes occurred before the onset of puberty, have higher chances of developing autoimmune diseases of the thyroid gland (OR= 3.0; (95% CI 1.1-7.6), p= 0.02).

Discussion

According to global data, 17-30% of patients with T1DM have autoimmune diseases of the thyroid gland, and at the time of diagnosis, about 25% of children with T1DM have autoantibodies to the thyroid gland (Ridha, & Al Zubaidi, 2019; Triolo et al., 2011). Our research shows that 15.8% of children have T1DM combined with autoimmune disorders of the thyroid gland and are consistent with the data of other authors regarding the high prevalence of AITD among patients suffering from T1DM (Mäkimattila et al., 2020; Kakleas et al., 2021; Al-Khawari, Shaltout, Qabazard, Al-Sane, & Elkum, 2015; Ogarek, Mrówka, & Jarosz-Chobot, 2021).

The conducted research is also fully consistent with the opinion that the female sex is a risk factor for the development of autoimmune diseases, in particular, the thyroid gland (Shun et al., 2014; Fatourechi et al., 2017; Orzan et al.,2016). In our research, we also found that the frequency of AITD depends on gender and is significantly higher in girls. In addition, the frequency of autoimmune disorders among girls and boys completely coincides with the data.

Unlike the research of Kakleas at al. (2021), we did not establish a probable connection between autoimmune disorders of the thyroid gland in children and adolescents and the duration of diabetes [18]. This is likely due to the wider age range of children participating in the research by Kakleas at al. (2021) – from 2 to 20 years old, while in our research children from 8 to 18 years old participated.

Meanwhile, like Kakleas at al. (2021), we observed a statistically significant higher risk of developing autoimmune thyroid disorders in pubertal children compared to children under 9 years of age in contrast to the research of Al-Khawari M. et al. (2015), who showed the early appearance of thyroid antibodies, during the first 5 years from the onset of diabetes. At the same time, our research shows that it is the manifestation of T1DM at a younger age, and not the duration of T1DM, that is a risk factor for the development of autoimmune thyroid diseases.

Conclusion

In 15.8% of children with T1DM, increased levels of anti-TPO are observed. Increased levels of antithyroid antibodies are associated with female gender, age at puberty, and prepubertal manifestation of T1DM. This confirms the need for screening children and adolescents with T1DM for antibodies and antigens of the thyroid gland in accordance with international recommendations. Determination of anti-TPO, especially in girls and children who have developed T1DM in childhood or prepubertal age, will contribute to the timely detection of autoimmune thyroid dysfunction and improve the course of T1DM in children and adolescents.

Conflicts of Interest

There is no conflict of interest that could cause the research to be biased.

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