Epidemiology and Clinical Characteristics of Thyroid Dysfunction in Children and Adolescents with Type 1 Diabetes

Severinski, Srećko; Banac, Srđan; Smiljan Severinski, Neda; Ahel, Vladimir; Cvijović, Katarina

Source / Izvornik: **Collegium antropologicum, 2009, 33, 273 - 279**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:344004

Coll. Antropol. **33** (2009) 1: 273–279
Professional paper

Epidemiology and Clinical Characteristics of Thyroid Dysfunction in Children and Adolescents with Type 1 Diabetes

Srećko Severinski[1], Srđan Banac[1], Neda Smiljan Severinski[2], Vladimir Ahel[3] and Katarina Cvijović[1]

[1] Pediatric Clinic, University Hospital Center »Rijeka«, Rijeka, Croatia
[2] Clinic for Gynecology and Obstetrics, University Hospital Center »Rijeka«, Rijeka, Croatia
[3] Department of Oral and Maxillofacial Surgery, University Hospital Center »Rijeka«, Rijeka, Croatia

A B S T R A C T

The aim of the study was to evaluate the natural course and potential risk factors of autoimmune thyroiditis (AIT) and thyroid dysfunction, and their influences on growth and glycemic control in children and adolescents with type 1 diabetes mellitus (T1D). The study comprised 148 subjects (age range 1–21 years; males 51%) with T1D. During the interval of 12 years serum levels of thyroid peroxidase (anti-TPO) and thyroglobulin (anti-TG) autoantibodies, thyroid-stimulating hormone (TSH) and tyroksine (T4), were screened annually. Height, weight, body mass index (BMI), glycosylated hemoglobin (HbA1c), insulin dose and the number of severe hypoglycemic episodes, were recorded every 3 months.The mean folow-up was 7 ± 4.1 years. Prevalence of AIT in subjects with T1D was 15.5%. It was significantly higher in girls (21.9% vs. 9.3%; p=0.03). The mean age at AIT onset was 11.5 ± 5.2 years. The mean interval between negative and positive AIT screening was 2.5 ± 2.3 years. Cumulative incidence of AIT after 6 years of T1D duration was significantly higher in girls (30% vs. 15%; p=0.03). Prevalence of hypothyroidism was 8.1% with no significant differences in sex distribution. Prevalence of hypothyroidism among subjects with elevated serum thyroid antibodies was 52.2% with significant male preponderance (85.7% vs. 37.5%; p=0.005). There were no subjects who developed hypothyroidism in absence of thyroid antibodies. Cumulative incidence of hypothyroidism after 3 years from the moment of thyroid antibodies appearance was 55% with significant male preponderance (85% vs. 40%; p=0.005). The mean interval between T1D onset and hypothyroidism development was 3.3 ± 2.5 years, and between thyroid antibodies appearance and hypothyreoidism development was 1.7 ± 1.2 years. The mean age at hypothyroidism onset was 12.7 ± 5.3 years. There were no differences in growth and metabolic control between patients with and without AIT. The results of the present study confirmed frequent occurrence of AIT and thyroid dysfunction in subjects with T1D. The number of newly diagnosed subjects with AIT reached the peak at the age of puberty. Girls were significantly more predisposed to AIT at any age while amongst subjects with elevated thyroid antibodies boys developed hypothyroidism more frequently. Annual screening of thyroid antibodies in all patients with T1D is recommended, while serum TSH level should be measured in patients with detected thyroid antibodies.

Key words: *type 1 diabetes mellitus, autoimmune thyroid disease, childhood*

Introduction

Type 1 diabetes mellitus (T1D) is often associated with the presence of other autoimmune diseases. Amongst them, autoimmune thyroiditis (AIT) has the most frequent occurence[1,2]. Elevated serum level of antibodies against thyroperoxidase (anti-TPO) and thyroglobulin (anti-TG) is a distinctive abnormality that permits a presumptive diagnosis of AIT[3]. AIT is often clinically silent but it may progress to autoimmune thyroid disease (AITD) characterized by either overt or subclinical presentation of hypothyroidism or hyperthyroidism[4–6]. The reported prevalence rates of AIT in children and adolescents with T1D vary from 3,9 to 50%[7–12].

Received for publication July 1, 2008

These results are in contrast to low AIT prevalence of 3,4–4,5% found in general population[13,14].

A detailed understanding of natural course of AIT associated with T1D is still lacking and there are many questions to be answered about it: Which of the diseases precedes in the course, T1D or AIT? What proportion of the patients with T1D have elevated serum level of thyroid antibodies, and how many of them will develop thyroid disfunction? When do these events occure in course of T1D?

Furthermore, the role of possible risk factors, such as patient's age and sex, duration of T1D and presence of thyroid antibodies, for development of AIT and thyroid disfunction in children and adolescents with T1D has to be elucidated too.

Due to a small number of performed studies there has been little insight into the epidemiological aspects and natural course of AIT associated with T1D. Therefore, existing recommendations considering diagnostic detection of AIT and thyroid disfunction in patients with T1D vary remarkably.

According to the International Society for Pediatric and Adolescent Diabetes (ISPAD) investigation of thyroid function and detection of thyroid antibodies should be performed at the onset of diabetes, and should be repeated only in case of emerging symptoms suggesting thyroid disfunction[15]. Thus, screening of asymptomatic patients is not recommended by ISPAD.

On the other hand, American Diabetes Association (ADA) recommends TSH screening at the onset of diabetes and following its stabilisation. TSH screening should also be performed later if symptoms of hypo or hyperthyroidism are suspected. In case of confirmed hypo or hyperthyroidism screening should be repeated once a year or every two years[1]. According to ADA neither screening of thyroid antibodies nor screening of thyroid function in clinically euthyroid patients with positive antibodies are recommended.

Furthermore, there are conflicting reports on possible influence of AIT upon growth and development, and metabolic control in diabetic patients. Some results showed that thyroid dysfunction has no influence on BMI, lipidemia and HbA1c[4,16,17], whereas there are opposite reports showing a significant impairment of glycemia caused by thyroid dysfunction[1]. Hyperthyroidism can result in a sudden increase of HbA1c[18], and hypothyroidism, even if subclinical, can be associated with significant risk for the development of symptomatic hypoglicemia[19], growth delay[20], weight gain, menstrual abnormalities, and poor condition in general[21]. Moreover, hypothyroidism can lead to hyperlipidemia and its cardiovascular complications which have more frequent occurence in diabetic patients anyway[22,23]. In order to prevent all these complications early diagnosis of AIT and thyroid dysfunction is esential.

The aim of this study was to evaluate some epidemiological and clinical aspects of AIT and thyroid dysfunction, includnig potential risk factors for their onset, in children and adolescents with T1D. Their influence on growth and glycemic control in diabetic patients was also analysed. After all, recommendations considering an efficient screening of AIT in children and adolescents with T1D were provided.

Patients and Methods

The study comprised 148 children and adolescents suffering from T1D. Their age ranged 1–21 years, and they showed an equal sex distribution (75 males; 50.7 %). Their mean age at the time of T1D diagnosis was 9.5 (± 4.2) years with the range of 1.3–17.9 years. All the patients included in the study were diagnosed and managed at the Paediatric Clinic, Clinical Hospital Center Rijeka, between Jannuary 1995. and Jannuary 2005. Their mean follow up was 7.0 ± 4.1 years. The diabetic patients were regularly screened for AIT and thyroid dysfunction once a year, and according to the results they were divided in two groups: the group with and the group without associated AIT.

Diagnostic detection of AIT was performed by measuring anti-TG and anti-TPO concentrations in serum using chemiluminescent sequential immunometric assay IMMULITE Anti-TG Ab and Anti-TPO Ab, DPC, Los Angeles, USA. The reference values were: <40 IU/mL for anti-TG, and <35 IU/mL for anti-TPO. The serum levels of thyroid antibodies >100 IU/mL were considered to be significantly increased. Thyroid function was determined by measurement of serum TSH and T4 using immunoradiometric assay BRAHMS, Hennigsdorf, Germany. The reference values were: 0.3–5.0 mIU/L for TSH, and 58–154 nmol/L for T4. In case of thyroid dysfunction and/or presence of thyroid antibodies ultrasonography was performed because the finding of hypoechogeneous and inhomogeneous structure of usually enlarged thyroid gland is typical for AIT[16].

Patients with T1D underwent regular examinations, at least every three months, which included measurements of hight and weight, and calculation of BMI. The z-score for height and BMI was calculated based on the Zurich longitudinal growth data[24]. In addition, insulin dose (U/kg), number of severe hypoglycemic episodes (events/diabetes year) and glycosylated hemoglobin (HbA1c), were recorded. Measurement of HbA1c was performed using chromatographic spectrophotometry by Byo Systems, Barcelona, Spain, with the reference range of 4–6 % for non-diabetics.

Statystical analysis was performed using MedCalc Software, Mariakerke, Belgium, and Statistica, StatSoft, USA. Group comparisons were performed using t-test, χ^2-test, and Man-Whitney U-test. Data are presented as mean ± SD for normally distributed variables or as median and range for nongaussian distributed parameters. Kaplan-Meier analysis was used to calculate and to compare cumulative incidence among the study groups. Significant differences were assumed at a value of $p<0.05$.

Results

Calculated prevalence rate of AIT in children and adolescents suffering from T1D was 15.5% (23 of 148). The female/male ratio was 2.3:1 suggesting significantly (p= 0.03) more frequent occurence of AIT in female (16 of 73; 21.9%) than in male (7 of 75; 9.3%) patients.

Anti-TPO and anti-TG were detected in 21 (14.2%) and 17 (11.5%) patients respectively. The mean age of AIT onset was 11.5 ± 5.2 years, ranging 1.5–18.5 years. The mean interval between negative and positive results of AIT screening was 2.5 ± 2.3 years, ranging 0–6.1 years.

There were 8 patients with AIT at initial screening and 15 patients developed AIT in the course of the next six years. Afterwards, there were no newly diagnosed diabetic patients with AIT (Figure 1).

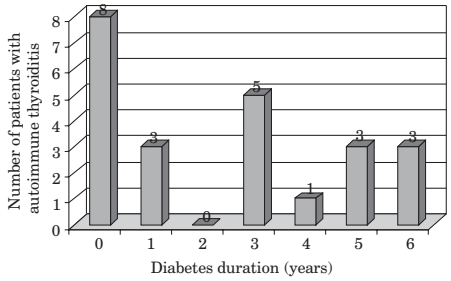

Fig. 1. The number of newly diagnosed patients with autoimmune thyroiditis in relation to type 1 diabetes duration.

Cumulative incidence rate of AIT in all patients after six years of diabetes duration was 22% (Figure 2A). It was significantly (p=0.0254; hazard ratio 0.3823; 95% CI 0.169 to 0.89) higher in female (30%) than in male (15%) patients (Figure 2B).

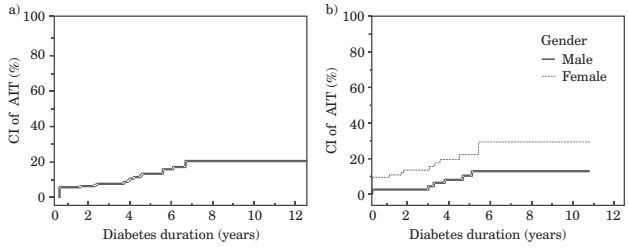

Fig. 2. Kaplan Meier curve shows probability of autoimmune thyroiditis (AIT) onset, or cumulative incidence(CI) in relation to the duration of type 1 diabetes in all patients (A), and according to the gender (M=male; F=female) (B).

There was no significant difference (p=0.91) of the mean age of T1D onset between patients with (10 ± 4.9 years) and without (9.9 ± 4.2) associated AIT.

The apparition of AIT became more frequent as patients became older. The peak of AIT occurence fell into the age group 11–15 years (p=0.03) (Figure 3).

Hypothyroidism was present in 12 (8.1%) of all 148 diabetic patients. There were 6 male (8.0% of all male diabetics) and 6 female (8.2% of all female diabetics). There were any patients with hyperthyroidism.

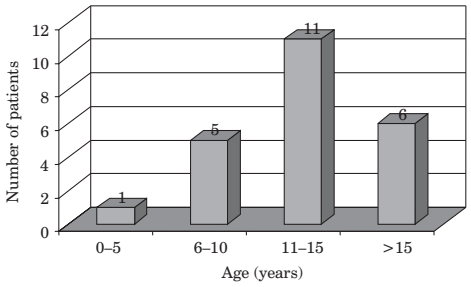

Fig. 3. The number of diabetic patients with autoimmune thyroiditis increased along with their age.

Hypothyroidism developed in 12 of 23 (52.2%) patients with positive finding of thyroid antibodies. There were no diabetic patients with hypothyroidism and simultaneously being negative for thyroid antibodies.

The mean interval between T1D onset and development of hypothyroidism was 3.3 ± 2.5 years. The mean interval between appearance of thyroid antibodies and development of hypothyrodism was 1.7 ± 1.2 years. Hypothyroidism developed at the mean age of 12.7 ± 5.3 years, ranging 1.5–19.3 years.

Among the diabetic patients with positive finding of thyroid antibodies hypothyroidism showed significantly more (p<0.01) frequent occurrence in males. In other words, 6 of 7 (85.7%) male patients with positive finding of thyroid antibodies, in analogous comparison to only 6 of 16 (37.5%) female patients, developed hypothyroidism.

There is no significant difference (p=0.34) in the mean age of T1D onset between the patients with and without hypothyroidism. The patients with positive finding of thyroid antibodies were followed up for 8.0 ± 3.6 years. The mean age of T1D onset in those who remained euthyroid was 11.9 ± 5.0 years in comparison to the mean age of 8.45 ± 5.8 years of patients who developed hypothyroidism.

Cumulative incidence rate of hypothyroidism in all diabetic patients, 3.5 years following the moment of thyroid antibodies detection, was 55 %. Afterwards, there were no newly diagnosed patients with hypothyroidism (Figure 4A).

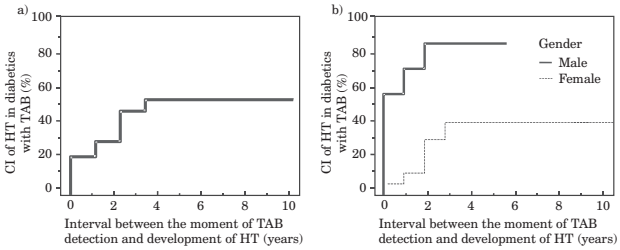

Fig. 4. Kaplan Meier curve shows probability, or cumulative incidence (CI) of hypothyroidism (HT) in relation to elevated antithyroid antibodies(TAB) in all diabetic patients (A), and according to the gender(B). Thus, these are intervals between the moment of TAB detection and development of HT.

Cumulative incidence rate of hypothyroidism was significantly (p<0.01; hazard ratio 3.8386; 95% CI 1.939 to 43.5512) higher in male (85 %) than in female (40 %) patients. At the initial screening the cumulative incidence rate was 57 % in males, in comparison to only 6 % in females. Cumulative incidence showed an increased tendency in females reaching the rate of 40 % three years later. On the other hand, cumulative incidence of hypothyroidism in males reached the peak 2.5 years following the moment of thyroid antibodies detection (Figure 4B).

There were 2 patients with hypothyroidism at initial screening of thyroid antibodies, and 10 patients developed hypothyroidism in the course of the next four years. Afterwards, there were no newly diagnosed diabetic patients with hypothyroidism (Figure 5).

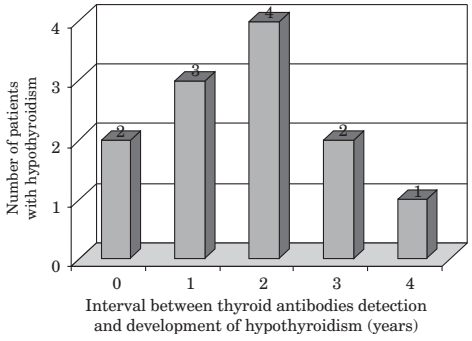

Fig. 5. The number of newly diagnosed diabetic patinets with hypothyroidism in relation to presence of thyroid antibodies.

There was an increasing trend of the number of newly diagnosed diabetic patients with hypothyroidism showed an increasing trend as they became older, but not in a significant manner (p=0.34) (Figure 6).

Anti-TG were negative in 5 of 12 patients with hypothyroidism in comparison to anti-TPO which were detected in 11 of 12 patients with thyroid dysfunction. Thus, anti-TG showed less sensitivity (58%) than anti-TPO which could predict the development of thyroid dysfunction with 92 % of sensitivity.

There was no significant difference (p=0.06) in thyroid function between the patients with low (100–1000 IU/mL) and high (>1000 IU/mL) serum level of thyroid antibodies.

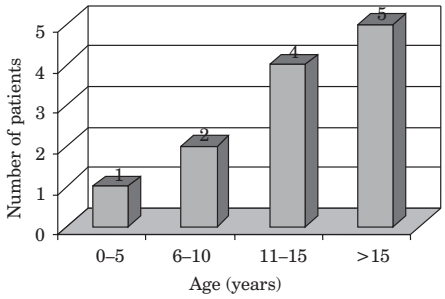

Fig. 6. The age at onset of hypothyroidism in diabetic patients wit autoimmune thyroiditis.

Ultrasonographic finding of thyroid gland was abnormal in majority of diabetic patients with AIT (n=21/23). However, there was no significant difference (p=0.054) between hypothyroid and euthyroid patients with AIT.

There is no significant difference in height, in BMI, in insuline dose and in the number of severe hypoglycemic episodes between the diabetic patients with or without associated AIT (Table 1).

Discussion

The results of this study showed that the prevalence of AIT and AITD is higher among children and adolescents suffering from T1D than in general population[13,14,25]. This is in accordance with results of many similar studies with reported prevalence rates of AIT in diabetic patients varying from 15 to 20%[9,16,26–28].

The lowest prevalence rate of AIT in diabetic children of 3.9% was reported by authors from Italy, Austria and Croatia more than a decade ago. This was an international multicentric study which included investigators of the present study too. At that period the reported prevalence rate of AIT in Croatian diabetic children was 11.8%[7]. The very highest prevalence of AIT in diabetic patients was reported by Burek. He found the prevalence rate of detected thyroid antibodies to be even 50% among caucasian children and adolescents suffering from T1D in USA[12]. The reason for such expressive variations of

TABLE 1
CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF PATIENTS WITH TYPE 1 DIABETES WITHOUT AND WITH AUTOIMMUNE THYROIDITIS

	Patients with T1D without AIT N=125; X ± SD	Patients with T1D and AIT N=23; X ± SD	p
Height SD score	0.47 ± 0.9	0.14 ± 0.9	0.16
BMI SD score	0.1 ± 0.7	0.11 ± 0.8	0.73
Insulin dose (units/kg/day)	0.7 ± 0.4	0.8 ± 0.3	0.39
HbA1c (%)	8.1 ± 1.7	8.5 ± 0.5	0.12
Severe hypoglycemias (events/diabetes year)	0.3 ± 0.36	0.4 ± 0.34	0.33

T1D – type 1 diabetes mellitus, AIT – autoimmune thyroiditis, BMI – body mass index, HbA1c – glycosylated hemoglobin

AIT prevalence in diabetics could probably be explained by genetic factors along with a lack of methodological uniformity concerning thyroid antibodies detection. The lower prevalence rates reported in earlier studies could have been a consequence of available less sensitive diagnostic tests though there might be a real increase of AIT incidence over the last few decades.

In the majority of published studies female sex was emphasized as one of the most important risk factors for development of AIT and thyroid dysfunction in diabetic patients. The usual reported female/male ratio seems to be 2–3:1[9,27,29,30], but there are some studies which did not find significant sex distribution among diabetic patients with associated AIT[4,16,26]. The present study confirmed significantly more frequent occurrence of AIT in female diabetics while the prevalence of hypothyroidism was equally distributed between sexes. However, in the group of patients with positive thyroid antibodies hypothyroidism developed more frequently in male patients. This result is in contrast to existed published data which showed female preponderance in this group of patients. Even in general population of children and adolescents with the reported prevalence of thyroid antibodies of 3.4%, there is a female preponderance with female/male ratio 2.7:1[13]. More frequent occurrence of AIT in females is attributed to hormone influences[31].

Thyroid antibodies are indicators of the presence of AIT which is usually asymptomatic, but it can evolve to subclinical or manifest, hypo or hyperthyroidism[4,5,32].

There is a question about dynamism of thyroid antibodies apparition and development of thyroid dysfunction. Are these events under the influence of patient's sex and age, or they are affected by duration of T1D?

According to research data hypothyroidism evolve in 4–68 % of patients with T1D, but only in 5–10% of subjects in general population. It has a higher prevalence in older people and in women in both groups[4,5,7,11,26–30,33–37].

The present study showed that thyroid antibodies were detected in the majority of patients at the inital screening. This is in accordance with many studies reporting a high proportion of diabetic patients with AIT who were detected at the very beginning of T1D. Gonzales detected anti-TPO in 14.2% of patients at the beginning of T1D, and reported on 68% of patients who developed hypothyroidism subsequently[30]. According to Franzese 55% of patients had elevated serum levels of thyroid antibodies at the initial screening. In others thyroid antibodies were detected after the mean interval of T1D duration of 7 years. Hypothyroidism evolved in 14,3% of patients with AIT[27]. Umiperez has also reported that in the majority of patients thyroid antibodies were detected at the beginning of the study, and only one patient became positive 12 years later[4]. The incidence rate of AITD of 0.91 on 100 patient's years was reported by Glastras[11]. Progresion to hypothyroidism in patients with positive thyroid antibodies occurs in 5–7%/year and in 20–24%/year in elderly patients[38,39].

The mean interval between negative and positive results of thyroid antibodies was similar to the mean interval of 2.8 years stated in literature data[11]. The calculated values of the mean intervals between T1D onset and development of hypothyroidism, between thyroid antibodies detection and development of hypothyroidism, and the median age of hypothyroidism onset, have also showed a good correspondance when comparing the results of the present study and literature data[5,9].

Investigators that included T1D patients of all ages, reported somewhat longer period of time needed for hypothyroidism development[4,30].

There are seldom studies in children that included calculation of cumulative incidence or probability of AIT appearance. One of such studies showed that cumulative incidence of AIT at the age of 18 years was 14% in all subjects suffering from T1D, with a significant female predominance. Cumulative incidence of AIT after 10 years of T1D duration was 14%, and its rate again was significantly higher in girls[9].

In the present study the peak of AIT cumulative incidence was reached after 6 years of T1D duration with significantly higher rate in girls. During the next 6-year period of follow-up there were no newly diagnosed patients with AIT. Girls were more predisposed to AIT at any age.

In the study conducted by Kordonouri subjects were attended for 15 years of T1D duration. The peak of AIT cumulative incidence was reached by boys after 10 years of T1D duration in comparison to 13 years in girls[9].

In the present study, the interval between appearance of thyroid antibodies and hypothyroidism was represented as cumulative incidence. Its peak was reached 3.5 years following the appearance of thyroid antibodies. Cumulative incidence of hypothyroidism was significantly higher in boys than in girls. At the initial screening the cumulative incidence rate in boys exceeded by far the one in girls. However, the latter rate increased subsequently reaching its peak 3.5 years later. The peak of hypothyroidism cumulative incidence was reached in boys 2.5 years following the appearance of thyroid antiboides. Although the follow-up of subjects continued for ten years it is interesting to notice that after 3.5 years from the moment of thyroid antibodies detection there were no newly registered cases with hypothyroidism.

Since the literature data are in contradiction, there is a question concerning the age at onset of T1D as a possible risk factor for more expeditious evolution of AIT and AITD. The results of the present study showed no significant differences of subjects age at T1D onset between the patients with and without AIT, as well as between the patients with or without thyroid dysfunction. These results are in accordance with many published reports[5,11]. On the other hand, there are authors with different conclusions suggesting that AIT prevalence decreases along with the increasing age at T1D onset[40], or that the age at T1D onset was significantly higher in the group of diabetic patients with an early appearance of AIT in com-

parison to the patients who developed AIT later, or to the diabetic patients who did not develop AIT at all[27]. Gonzales reported that the diabetic patients who developed hypothyroidism had met with the onset of T1D at their older age[30].

Many investigators found by far more frequent occurence of hypothyroidism in diabetic patients in the presence of thyroid antibodies[4,9,11,30]. There were any patients in the present study that developed hypothyroidism in the absence of thyroid antibodies. It is worth to remark that, in addition to the obligatory iodine supplementation of salt, Croatia is not an iodine-deficient area.

In accordance with many other reports[30,41,42] there was greater proportion of detected anti-TPO than anti-TG in presented diabetic patients with AIT. Furthemore, anti-TG showed to be less sensitive marker, than anti--TPO, who developed hypothyroidism. Thus, anti-TG seems to be of less usefulnesss in predicting thyroid dysfunction[42]. Still, thyroid antibodies can predict thyroid dysfunction in children suffering from T1D with sensitivity of 50% and with specificity of 84%[28]. According to Gonzales anti-TG showed less sensitivity than anti-TPO. The latter antibodies can predict thyroid dysfunction with 95% of sensitivity and with 96% of specificity[30]. There are rare reports suggesting an equal sensitivity of both thyroid antibodies[9].

The results in the present study showed that there were no significant differences in thyroid dysfunction between the groups of patients with mild (100–1000 IU/mL) and high (>1000 IU/mL) serum elevation of thyroid antibodies. However, there are some reports suggesting that a mild serum elevation of thyroid antibodies does not lead to hypothyroidism as it happened in 75% of patients with high serum levels of thyroid antibodies[43]. Thus, there seems to exist a certain degree of correlation between high serum levels of thyroid antibodies and development of hypothyroidism[5].

The presented results showed that ultrasonographic findings of thyroid gland were not normal in almost all our patients with AIT. But, there were any significant differences in thyroid ultrasonography between AIT subjects with and without thyroid dysfunction. According to literature data only 10% of children with mild, and even 83% of children with high serum levels of thyroid antibodies had developed ultrasonographic signs typical for AIT[43]. Kordonouri reported that 87.5% of patients with AIT, and all the patients with AITD showed certain ultrasonographic changes of thyroid gland[5,9].

Comparisons of weight, BMI, insulin dose, HbA1c and the number of severe hypoglycemic episodes between diabetic patients with and without AIT did not present with significant differences in the present and in many other similar studies[4,16,17,29,33]. We assume that possible complications were prevented because of frequently performed AIT screening that resulted in early recognition of the disease. Nevertheless, some studies have showed that patients with hypothyroidism had significantly more symptomatic hypoglycaemic episodes during the 12 months before diagnosis, incresing progressively during thise time period and reaching a peak at the moment of diagnosis[19]. Moreover, it has been suggested that recurrent hypoglycaemia is a presenting sign of underlaying hypothyroidism[44]. The consensus guidelines 2000 of ISPAD (International Society for Paediatric and Adolescent Diabetes) suggest that hypothyroidsm might influence metabolic control[45]. It seems that growth potential among people with Type 1 diabetes and subclinical hypothyroidsm may be significantly reduced[20].

Conclusion

The results of the present study confirmed frequent occurrence of AIT and AITD in children and adolesents suffering from T1D. The number of newly diagnosed patients with AIT reached the peak at the age of puberty. Girls were significantly more predisposed to AIT at any age. Among the patients with serum elevated thyroid antibodies AITD showed to be significantly more frequent in boys. There was no relation between the rate of thyroid antibodies serum elevation and thyroid dysfunction, as there were no differences in growth and metabolic control between patients with and without AIT. Annual screening of thyroid antibodies, particularly anti-TPO, in all children and adolescents with T1D is recommended. The serum TSH level should be measured in all patients with serum elevated thyroid antibodies.

REFERENCES

1. SILVERSTEIN J, KLINGENSMITH G, COPELAND K, PLOTNICK L, KAUFMAN F, LAFFEL L, DEEB L, GREY M, ANDERSON B, HOLZMEISTER LA, CLARK N, Diabetes Care, 28 (2005) 186. — 2. SLOVER RH, EISENBARTH GS, Endocrine Rev,18 (1998) 241. — 3. DALLAS JS, FOLEY TP, Thyromegaly. In: LIFSHITZ F (Ed) Pediatric Endocrinology (Marcel Dekker, New York -Basel, 2003). — 4. UMIPEREZ GE, LATIF KA, MURPHY MB, LAMBERTH HC, STENTZ F, BUSH A, KITBACHI AE, Diabetes Care, 26 (2003) 1181. — 5. KORDONOURI O, DEISS D, DANNE T, DOROW A, BASSIR C, GRÜTERS KIESLICH A, Diabetic Medicine, 19 (2002) 518. — 6. DAYAN CM, DANIELS GH, N Engl J Med, 335 (1996) 99. — 7. RADETTI G, PAGANINI C, GENTILI L, BERNASCONI S, BETTERLE C, BORKENSTEIN M, CVIJOVIC K, KADRNKA-LOVRENCIC M, KRZISNIK C, BATTELINO T, LORINI R, MARINONI S, RIGON F, TATO L, PINELLI L, TONINI G, Acta Diabetol, 32 (1995) 121. — 8. HANUKOGLU A, MIZRACHI A, DALAL I, ADMONI O, RAKOVER Y, BISTRITZER Z, LEVINE A, SOMEKH E, LEHMANN D, TUVAL M, BOAZ M, GOLANDER A, Diabetes Care, 26 (2003) 1235. — 9. KORDONOURI O, HARTMANN R, DEISS D, WILMS M, GRÜTERS-KIESLICH A, Arch Dis Child, 90 (2005) 411. — 10. EISENBARTH GS, GOTTLIEB PA, N Engl J Med, 350 (2004) 2068. — 11. GLASTRAS SJ, CRAIG ME, VERGE CF, CHAN AK, COSUMANO JM, DONAGHUE KC, Diabets Care, 28 (2005) 2170. — 12. BUREK CL, ROSE NR, GUIRE KE, HOFFMAN WH, Autoimmunity, 7 (1990) 157. — 13. KABELITZ M, LIESENKOTTER KP, STACH B, WILLGERODT H, STÄBLEIN W, SINGENDONK W, JÄGER-ROMAN E, LITZENBÖRGER H, EHNERT B, GRÜTERS A, European Journal of Endocrinology, 148 (2003) 301. — 14. What is diabetes? Available from: . ISPAD. Consensus guidelines for the management of type 1 diabetes mellitus in children and adolescents. (Zeist, Netherlands: Medforum, 2000.) — 16. HANSEN D, BENNEDBAEK FN, HOIER-MADSEN M, HEGEDÜS L, JACOBSEN

BB, European Journal of Endocrinology,148 (2003) 245. — 17. HOLL RW, BÖHM B, LOOS U, GRABERT M, HEINZE E, HOMOKI J, Horm Res, 52 (1999) 113. — 18. PRAZNY M, ŠKRHA J, LIMANOVA Z, VANIČKOVA Z, HILGERTOVA J, PRAZNA J, JAREŠOVA M, STRIŽ I, Physiol Res, 54 (2005) 41. — 19. MOHN A, DI MICHELE S, DI LUZIO R, TUMINI S, CHIARELLI F, Diabet Med, 19 (2002) 70. — 20. CHASE HP, GARG SK, COCKERHAM RS, WILCOX WD, WALRAVENS PA, Diabet Med, 7 (1990) 299. — 21. BARKER JM, J Clin Endocrin Metab, 91 (2006) 1210. — 22. GEUL KW, VAN SLUISVELD IL, GROBBE DE, DOCTER R, DE BRUYN AM, HOOYKAAS H, VAN DER MERWE JP, VAN HEMERT AM, KRENNING EP, HENNEMANN G, Clin Endocrinol, 39 (1993) 275. — 23. HAK AE, POLS HA, VISSER TJ, DREXHAGE HA, HOFMAN A, WITTEMAN JC, Ann Inetrn Med,132 (2000) 270. — 24. PRADER A, LARGO RH, MOLINARI L, ISSLER C, Helv Paediatr Acta, 52 (1989) 1. — 25. VANDERPUMP MP, TUNEBRIDGE WM, Thyroid, 12 (2002) 839. — 26. MANTOVANI RM, MANTOVANI LM, DIAS VM, J Pediatr Endocrinol Metab, 20 (2007) 669. — 27. FRANZESE A, BUONO P, MASCOLA M, LEO AL, VALERIO G, Diabetes Care, 23 (2000) 1201. — 28. MCKENNA MJ, HERSKOWITZ R, WOLFSDORF JI, Diabetes Care, 13 (1990) 801. — 29. MCCANLIES E, J Clin Endocrinol Metab, 83 (1998) 1548. — 30. GONZALES GC, CAPEL I, RODRIGUEZ-ESPINOSA J, MAURICIO D, DE LEIVA A, PEREZ A, Diabetes Care, 30 (2007) 1611. — 31. VOLPE R, Autoimmune thyroid disease. In: BRAVERMAN LE (Ed) Contempory Endocrinology: Disease of the thyroid (Humana Press, Towa NJ 1997). — 32. TOPLISS DJ, EASTMAN CJ, Med J Aust, 180 (2004) 186. — 33. KORDONOURI O, KLINGHAMMER A, LANG EB, GRÜTERS-KIESLICH A, GRABERT M, HOLL RW, Diabetes care, 25 (2002) 1346. — 34. KIM EY, SHIN CH, YANG SW, Autoimmunity, 36 (2003) 177. — 35. HOLLWELL JG, STAHELING NW, FLANDERS WD, HANNON WH, GUNTER EW, SPENCER CA, BRAVERMAN LE, J Clin Endocrinol Metab, 87 (2002) 489. — 36. TUNBRIDGE WM, EVERED DC, HALL R, APPLETON D, BREWIS M, CLARK F, EVANS JG, YOUNG E, BIRD T, SMITH PA, Clin Endocrinol,7 (1977) 481. — 37. CANARIS GJ, MANOWITZ NR, MAYOR G, RIDGWAY EC, Arch Intern Med, 160 (2000) 526. — 38. TUNBRIDGE WMG, BREWIS M, FRENCH JM, APPLETON D, BIRD T, CLARH F, BMJ, 282 (1981) 258. — 39. HELFAND M, CRAPO LM, Ann Intern med, 112 (1990) 840. — 40. GOODWIN G, VOLKENING LK, LAFFEL LMB, Diabetes Care, 29 (2006) 1397. — 41. VAKEVA A, KONTIAINEN S, MIETTINEN A, SCHLENZKA A, MAENPAA J, J Clin Pathol, 45 (1992) 106. — 42. MCLACHLAN SM, RAPOPORT B, Thyroid, 14 (2004) 510. — 43. RAKOSNIKOVA V, ZAHRADNIKOVA M, ZIKMUND J, PRUHOVA S, LEBL J, Cas Lek Cesk,142 (2003) 235. — 44. LEONG KS, WALLYMAHMED M, WILDING J, MACFARLANE I, Postgrad Med J, 75 (1999) 467. — 45. International Society for Pediatric and adolescent Diabetes. ISPAD 2000. Hypothyroidsm. In: Swift PGF ed. Consensus Guidelines 2000. Medical forum International, Zeist, 2000.

S. Severinski

Pediatric Clinic, University Hospital Center »Rijeka«, Istarska 43, 51000 Rijeka, Croatia
e-mail: sreckoseverinski@yahoo.com

EPIDEMIOLOGIJA I KLINIČKA OBILJEŽJA PORMEĆAJA RADA ŠTITNJAČE U DJECE I ADOLESCENATA OBOLJELIH OD ŠEĆERNE BOLESTI TIPA 1

S A Ž E T A K

Cilj rada je utvrditi tijek autoimunog tireoiditisa (AIT) i autoimune bolesti štitnjače (AITD) u djece i adolescentaa oboljelih od tip 1 šećerne bolesti (T1D) te čimbenike rizika za njihov razvoj. Također, analizirani su utjecaj AIT na rast, razvoj i metaboličku kontrolu dijabetičara. Istraživanje je obuhvatilo 148 djece i adolescenata s T1D, 50,7% muških (dob 1–21 g.) Od 1995. g., tijekom 12 godišnjeg razdoblja, jednom godišnje je učinjen probir na AIT mjerenjem koncentracije antitireoglobulinskih (anti-TG) i antitireoperoksidaznih antitijela (anti-TPO) i funkciju štitnjače mjerenjem tireotropnog hormona (TSH) i tiroksina (T4). Srednje vrijeme praćenja je bilo 7 ± 4,1 g. Na tromjesećnim kontrolama pacijentima se mjerila visina, masa i indeks tjelesne mase (BMI), bilježila se inzulinska doza, broj teških hipoglikemija te se određivao glikolizirani hemoglobin (HbA1c). Prevalencija AIT u djece i adolescenata oboljelih od T1D je 15,5% i češći je kod ženskih ispitanika, 21,9%:9,3% (p=0,03). Srednja dob javljanja AIT je 11,5 ± 5,2 g. Srednja dob intervala između negativnog i pozitivnog probira je 2,5 ± 2,3 g. Nakon 6 g. trajanja T1D kumulativna incidencija AIT je značajno viša u djevojčica (30%:15%) (p=0,0254). Prevalencija hipotireoze je 8,1% u svih pacijenata s T1D, nema značajne razlike među spolovima. Prevalencija hipotireoze je 52,2% u ispitanika sa pozitivnim antitireoidnim antitijelima. Niti jedan pacijent nije razvio hipotireozu ukoliko nije imao pozitivna antitireoidna antitijela. U bolesnika s pozitivnim antitireoidnim antitijelima hipotireoza je signifikantno viša u muških 85,7%:37,5% (p=0,0052). Kumulativna incidencija hipotireoze u oboljelih od T1D nakon 3 g. od pojave povišenih antitireoidnih antitijela je 55% i značajno je češća u dječaka nego u djevojčica 85%:40% (p=0,0052). Od početka T1D do razvoja hipotireoze srednje vrijeme je 3,3 ± 2,5 g. Od pojave pozitivnih antitireoidnih antitijela do razvoja hipotireoze srednje vrijeme je 1,7 ± 1,2 g. Srednja dob nastanka hipotireoze je 12,7 ± 5,3 g. Visina, BMI, inzulinska doza, HbA1c i učestalost teških hipoglikemija nisu se značajno razlikovali između skupine sa T1D bez i sa AIT. Utvrđena je visoka pojavnost AIT i AITD u djece i adolescenata sa T1D. AIT se značajno češće javlja u djevojčica u svakoj dobi. Među pacijentima sa povišenim antitireodnim antitijelaima, AITD je signifikantno češća u dječaka. Nema razlike u rastu, razvoju i kontroli glikemije u pacijenta sa i bez AIT. Naši rezultati sugeriraju godišnji probir u sve djece i adolescenata sa T1D na antitireoidna antitijela, naročito anti-TPO, a ispitivanje TSH u onih sa povišenim antitroidnim antitijelima.