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Coexisting psoriasis affects the clinical course of type 1 diabetes in children

Współistnienie łuszczycy wpływa na przebieg cukrzycy typu 1 u dzieci

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Abstract

Introduction. Literature reports link psoriasis with insulin resistance characteristic for type 2 diabetes. However, this condition may also affect the clinical course of type 1 diabetes (T1D). **Aim.** To investigate whether children with type 1 diabetes mellitus (T1D) and psoriasis have a different course of diabetes. **Methods.** We evaluated patients diagnosed with T1D in the years 2002-2011 for the presence of psoriasis and matched them 1:10 with T1D-only patients by sex and duration of diabetes using propensity score. We collected T1D-onset parameters and metabolic control surrogates from six months after T1D diagnosis. **Results.** We identified 14 patients with psoriasis and matched 140 controls, of whom 129 (68 boys) were eligible for the analysis. At onset T1D+psoriasis patients showed higher concentration of C-peptide than controls (median: 0.38ng/ml vs 0.15ng/ml, p=0.02). Six months later, they had non-significantly lower HbA1c (6.0 vs 6.6%, p=0.11), TC (143mg/dl vs 159mg/dl, p=0.14) HDL (54.5mg/dl vs 59mg/dl, p=0.11). **Conclusions.** Patients with T1D and psoriasis present higher endogenous insulin secretion at T1D onset and a tendency for better glycemic control during the first 6 months.

Key words

type 1 diabetes, children, psoriasis, c-peptide

Streszczenie

Wstęp. W doniesieniach literatury łuszczyca wiąże się z insulinoopornością, charakterystyczną dla cukrzycy typu 2. Potencjalnie stan ten może wpływać również na przebieg cukrzycy typu 1 (T1D). **Cel pracy.** Zbadanie, czy pacjenci pediatryczni z cukrzycą typu 1 i łuszczycą prezentują odmienny przebieg cukrzycy. **Materiał i metody.** Pacjenci z T1D zdiagnozowaną w latach 2002–2011 zostali retrospektywnie ocenieni w poszukiwaniu towarzyszącej łuszczycy. Do wyłonionej w ten sposób grupy dobrano kontrolę dzieci z samą T1D w stosunku 1:10 pod kątem płci i czasu trwania cukrzycy. Zebrano dane kliniczne z okresu rozpoznania cukrzycy oraz parametry wyrównania metabolicznego z wizyt kontrolnych po 6 miesiącach od rozpoznania cukrzycy. **Wyniki.** Zidentyfikowano 14 pacjentów z T1D i łuszczycą, dobrano 140 pacjentów z grupy kontrolnej, z których łącznie 129 (68 chłopców) włączono do analizy. W porównaniu do grupy kontrolnej pacjenci z T1D i łuszczycą charakteryzowali się wyższym stężeniem C-peptydu podczas rozpoznania T1D (mediana 0,38ng/ml vs 0,15ng/ml, p=0,02) oraz nieistotnie niższym stężeniem hemoglobiny glikowanej (6,0 vs 6,6%, p=0,11), całkowitego cholesterolu (143mg/dl vs 159mg/dl, p=0,14) i cholesterolu HDL (54,5mg/dl vs 59mg/dl, p=0,11) po 6 miesiącach od rozpoznania cukrzycy. **Wnioski.** Pacjenci z T1D i towarzyszącą łuszczycą wykazują wyższe stężenia endogennej insuliny w chwili rozpoznania cukrzycy oraz mają tendencję do lepszego wyrównania cukrzycy w trakcie pierwszych 6 miesięcy choroby.

Słowa kluczowe

cukrzyca typu 1, dzieci, łuszczyca, peptyd C

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Introduction

Autoimmune diseases are frequent, often chronic conditions in which the immune system fails to properly recognize autoantigens and targets them as pathogenic. When considered together, these diseases affect approximately 1 in 10 people [1], being one of the leading causes of disability, starkly affecting quality of life and draining medical budgets. In epidemiological studies, these conditions consequently cluster together, both in affected individuals [2] and their families [3].

It is important to study autoimmune diseases not only epidemiologically but also clinically. By comparing their course and presentation when occurring alone or in different constellations we may tell whether the observed phenotypes are classic for these diseases or not, for example milder or more severe. This, coupled with patients` family history, may help to select candidates for genetic testing and, possibly, uncover new gene candidates for those diseases. Type 1 diabetes and childhood-onset psoriasis are good candidates for such studies.

Type 1 diabetes is an autoimmune disease diagnosed almost exclusively in children, presenting with hyperglycemia and often ketoacidosis due to the lack of endogenous insulin secretion. It is caused by the destruction of β-cells of pancreas mediated by dendritic cells, macrophages, auto-reactive lymphocytes T CD4+ and T CD8+ that infiltrate pancreatic tissue [4]. It affects 0.027% of the population and 0.08% of European pediatric population [5].

Psoriasis is an immune-mediated inflammation of dermis and epidermis, which leads to keratinocytes hyperproliferation and presents as erythremous plaques covered by silvery lamellar scales [6,7]. Although it affects both pediatric and adult patients, in youth psoriasis has a distinct clinical presentation and is sometimes referred to as "type 1 psoriasis". Its prevalence in children varies across the populations, from low in the US (0.19–0.3%, California) to relatively high in European countries (0.55–1.37%, UK; 0.18–0.83%, Germany; 0.4–1.0%, the Netherlands) [8–10].

T1D and childhood psoriasis share similar ages of onset, around 8 for T1D [11] and 8–10 for psoriasis, according to various reports [12,13]. Importantly, in both diseases positive familial history is consistently reported. In children with T1D, 12.2% have an affected first-degree relative and 21.8% a first or second-degree relative [11]. In patients with psoriasis familial component is even more pronounced with 13.6% to 71% of children with an affected first-degree family member in different population studies [9,12,14]. So far there is no raw data on the co-occurrence of T1D and psoriasis but epidemiology shows that an individual diagnosed with an autoimmune disease has an elevated risk of developing another one [2]. Interestingly, in both conditions infection is proposed as a triggering factor. Moreover, recent studies report signaling molecules probably involved in the pathogenesis of T1D, psoriasis and obesity, namely interleukin 23 and 17 axis, interleukin 18 axis and microRNA (miR) miR-21 and miR-146a [15]. All of them are involved in chronic inflammation and physiology of adipocytes. These metabolic pathways may be clinically reflected by lipoproteins abnormalities. In our work we compared T1D and psoriasis as prominent examples of immune-mediated diseases with an environmental and familial component.

Aim

To compare the clinical course and lipid profiles of children affected with T1D and psoriasis versus ones with only T1D

Material and methods

Group and study design

From all children (<18 years old) hospitalized for T1D in the years 2002–2011 we chose those with T1D onset and at least one follow-up visit in this period. We screened them for confirmed or suspected psoriasis. T1D diagnosis was based on patient`s clinical presentation and significant presence of at least one type of autoantibody: glutamic acid decarboxylase (GADA), islet cell (ICA), insulin (IAA), insulinoma-associated-2 (IA2A) or Zinc Transporter 8 (ZnT8). Psoriasis was identified as mentioned in patient`s medical history and hospital discharge records. All patients with monogenic diabetes confirmed with sequencing or Multiplex Ligation-dependent Probe Amplification were excluded from the initial database. Next, we used logistic regression and propensity score matching to create a control group of children with only T1D; we matched them approximately 10 T1D: 1 T1D+psoriasis by gender and age at database entry.

The data were collected retrospectively. We searched medical histories for T1D onset parameters (age of onset, glycemia, presence of ketoacidosis and pH, fasting c-peptide concentration and autoantibody status). We also monitored the evolution of diabetes in our patients 6 months after the T1D diagnosis. From these records we derived metabolic control parameters: glycated hemoglobin (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoproteins (HDL), triglycerides (TG), body mass index (BMI) and insulin dosage per kilogram (ins/kg/24 hrs). HbA1c was measured by ion-exchange high-performance liquid chromatography (HPLC) ion-exchange HPLC (Variant Hemoglobin A1c Program; Bio-Rad Laboratories, Hercules, CA, USA). BMI was calculated using standard formula mass/height^2, with mass measured with the 100g accuracy (children were weighed light-clothed) and height with the 5mm accuracy. Triglycerides, total and HDL cholesterol concentrations were measured with a fluorometric method with an enzyme-coupled reaction using the Architect ci4100 device (Abbott Diagnostics, Wiesbaden, Germany). Fasting c-peptide was measured by radioimmunoassay and, since 2006, chemiluminescence). Autoantibody tests were performed in the reference laboratory of Immunopathology at the Department of Paediatrics, Oncology, Haematology and Diabetology, Medical University of Lodz, Poland. The conventional autoantibodies were

measured on serum samples: ICA with immunofluorescence, antibodies against GAD, IA2 and ZnT8 by enzyme-linked immunosorbent assay (RSR, USA) and insulin antibodies with radioimmunoassays (CisBiointernational, France and RSR, USA). The cut-off values for ICA, GADA, IA2A and IA/IAA positivity were10 Juvenile Diabetes Foundation units, 10U/ml and 20U/ml and 7% or 0,4U/ml respectively. Due to changes in kit providers across the timeline, all autoantibodieswere interpreted only as positive/negative according to appropriate cut-off points.

According to the Islet Autoantibody Standardization Program - IASP2015 the disease sensitivity of the antibody was ICA: 72,3%, GADA:82%, IA2A:70%, IA/IAA42% and ZnT8:76% respectively, while corresponding specificities were; ICA:94,4%, GADA:98,9%, IA2A:95,6%, IAA: 100% and ZnT8: 97,8%.

After data collection, BMI were transformed into z-score values based on charts for Lodz designed by Ostrowska-Nawarycz [16]. The metabolic control parameters were referred to the national and international guidelines issued respectively by the Diabetes Poland and the International Society for Pediatric and Adolescent Diabetes [17,18]. Additionally, we calculated the percentage of patients that presented partial remission defined after ISPAD criteria as HbA1c<7% with daily insulin dosage <0.5U/kg and after Diabetes Poland as HbA1c <6.4% and insulin demand <0.3U/kg/24h [17].

Statistical analysis

The groups were analyzed in terms of nominal variables using the two-tailed Fisher`s exact tests. Continuous variables were assessed with the Shapiro Wilk's test. As all variables significantly deviated from the normal distribution we decided to use the Mann-Whitney's U test and presented the data as medians and interquartile ranges (IQRs). In all analyzes, p values <0.05 were considered significant.

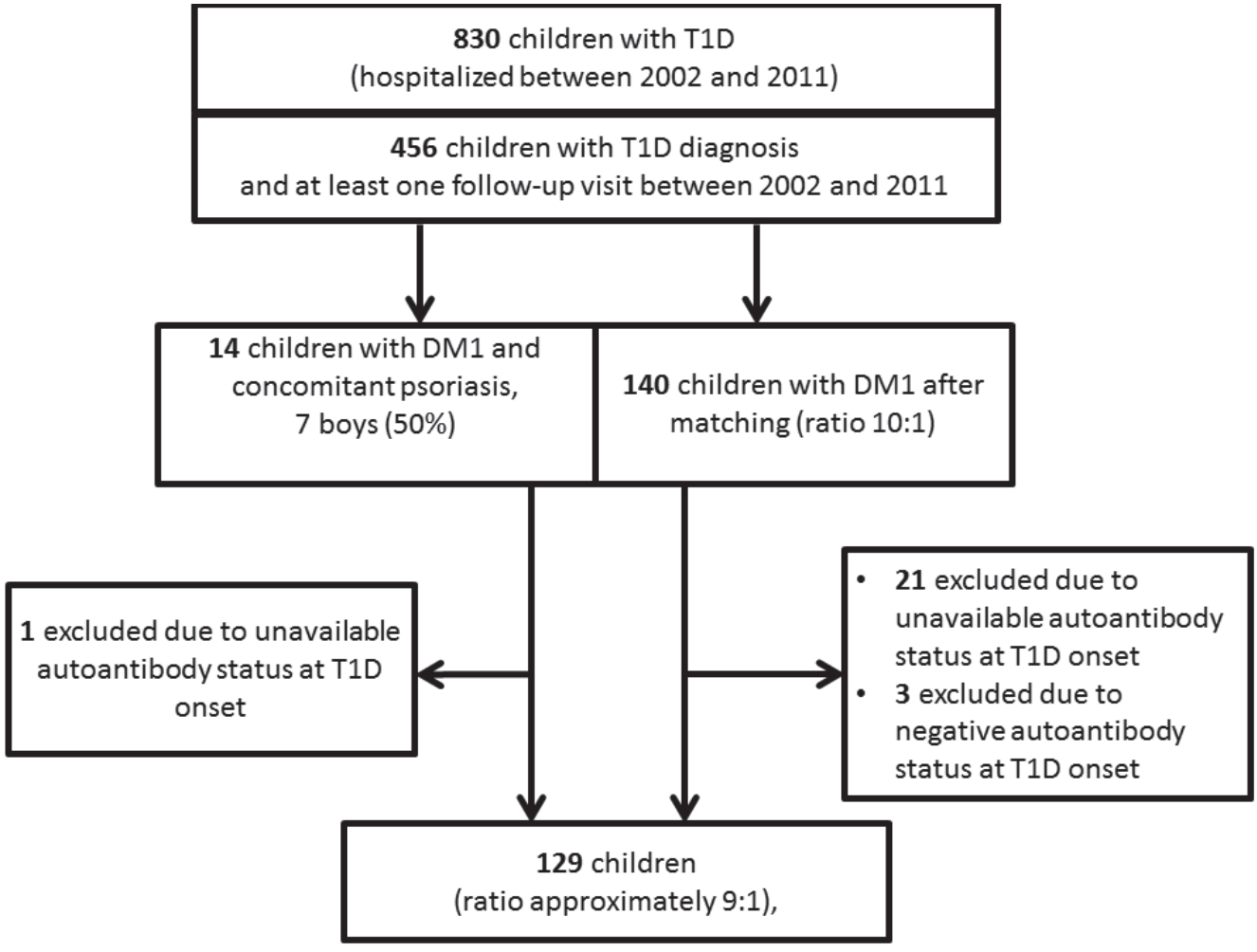

Fig. 1. Study design and patient selection
Ryc. 1. *Plan badania i dobór pacjentów*

Results

The initial database included patients from the years 2002–2011 and counted 830 children, out of which 465 had T1D onset and at least one follow-up in this period. Fourteen of those were found to have both T1D and psoriasis. Compared with T1D-only peers, the group with concomitant psoriasis had a similar gender distribution (p>0.05) but significantly higher age of T1D onset [median 11.9 years (interquartile range: 8.5 to 14 years) vs 6.9 years (IQR: 4.4 to 10.8 years)]. The matching procedure yielded 140 patients without psoriasis as a potential control group. After in depth clinical evaluation of the matched groups we excluded 22 children (1 with psoriasis, 21 with only T1D) due to an unknown antibody status at T1D onset and 3 patients (T1D-only) negative for all tested autoantibodies at T1D onset or incomplete medical records (fig. 1). The final study group eligible for analysis included 68 boys (52.7%) and 61 girls (47.3%) with median age of diagnosis 11.9 (IQR: 9.5–13.4) years. The T1D and psoriasis+T1D groups did not differ significantly in terms of gender and age of diagnosis (p>0.05).

Table I presents the summary of clinical characteristics at onset of T1D in the two matched groups of patients with T1D and psoriasis or T1D alone. Individuals from the former group had higher concentration of C-peptide at T1D onset than their peers with T1D only [median: 0.38 ng/ml (IQR: 0.16–0.48) vs 0.15 ng/ml (0.09–0.28), p=0.02]. The presence of ketoacidosis at T1D onset was similar between patients with and without psoriasis (69.2% vs 53.4%, p=0.37).

At T1D onset, all children were tested for 1 to 5 types of autoantibodies, depending on clinical justification, 10 patients for one, 28 for two, 35 for three, 36 for four and 20 for five respectively. At the time of testing, children with psoriasis and their peers showed similar frequencies of positive autoantibody results in each class (p>0.05).

Six months after the T1D diagnosis 27 patients met the criteria of partial remission by ISPAD and 9 by the Diabetes Poland. Remission frequency defined after ISPAD did not differ significantly between the groups (psoriasis – 40% vs T1D-only – 27.7%, p=0.47]. However, when considering more strict Polish guidelines, children with psoriasis achieved remission slightly more often (20% vs 8.4%, p=0.25). In terms of diabetes control, both groups had similar success rates in achieving targets set by the Diabetes Poland and ISPAD (p>0.05). Children with psoriasis showed a tendency to meet HbA1c therapeutic targets more often, but this difference did not meet statistical significance (Diabetes Poland: 66.7% patients in target versus 48.0%, p=0.36; ISPAD: 100% patients in target vs 80.4%, p=0.12).At the 6 month timepoint patients with T1D and psoriasis showed tendencies toward better glycemic control than children with T1D alone (median HbA1c 6% (IQR: 5.8%–6.8% vs 6.6% (IQR: 6.1%–7.4%), p=0.11), lower total cholesterol [143mg/dl (134mg/dl–170mg/dl) vs 159 mg/dl (145 mg/dl–181 mg/dl), p=0.14] and, in contrast to other results, lower HDL [(54.5 mg/dl (47 mg/dl–61 mg/dl) vs 59mg/dl (51mg/dl–71mg/dl), p=0.11] although these differences did not reach statistical significance due to the size of the studied group. Detailed comparison of metabolic control parameters is showed in **Table II.**

Discussion

Our results show that patients with T1D and psoriasis have an altered course of diabetes with later onset, less pronounced destruction of the beta cells and initially better metabolic control which seems to persist despite the patients having a tendency to gain more weight than their peers with T1D alone.

To date, very few studies have analyzed the relationship between psoriasis and T1D. More often than not psoriasis is

Table I. Comparison of clinical variables in children with concomitant psoriasis and standalone T1D at onset of diabetes. T1D – type 1 diabetes

Tabela I. *Porównanie danych klinicznych z czasu rozpoznania cukrzycy pomiędzy dziećmi z cukrzycą typu 1 oraz grupą z cukrzycą typu 1 i towarzyszącą łuszczycą. Me – median/mediana. T1D – cukrzyca typu 1*

	Psoriasis+T1D / Łuszczyca + T1D Median/mediana (25–75%)	T1D Median/mediana, (25–75%)	p value / wartość p
Age/ wiek (years) / (lata)	13.17 (8.55 to 13.95)	11.28 (9.53 to 13.34)	0.5186
Glycaemia / Glikemia (mg/dl)	429 (274 to 563)	436 (300 to 580)	0.7792
Fasting C-peptide concentration / Stężenie c-peptydu na czczo (pg/μl)	0.381 (0.165 to 0.480)	0.150 (0.090 to 0.280)	0.0171

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Table II. Comparison of medians of parameters of metabolic control between children with concomitant psoriasis and standalone T1D at 6 months of T1D duration. T1D – type 1 diabetes, HbA1c – glycated hemoglobin, TC – total cholesterol, HDL – high-density lipoprotein fraction of cholesterol, LDL – low-density lipoprotein fraction of cholesterol, TG – triglycerides, BMI z-score – body mass index z score, ins/kg – insulin per kg of body mass

Tabela II. *Porównanie parametrów kontroli metabolicznej cukrzycy pomiędzy dziećmi z cukrzycą typu 1 oraz grupą z cukrzycą typu 1 i towarzyszącą łuszczycą sześć miesięcy od rozpoznania cukrzycy. T1D – cukrzyca typu 1, HbA1c – hemoglobina glikowana, TC – cholesterol całkowity, HDL – frakcja lipoprotein o wysokiej gęstości, LDL – frakcja lipoprotein o niskiej gęstości, TG – trójglicerydy, BMI z-score – z-score dla indeksu masy ciała, ins/kg – dawka insuliny na kg masy ciała*

	Psoriasis+T1D / Łuszczyca + T1D Median / mediana (25–75%)	T1D Median / mediana, (25–75%)	p value / wartość p
HbA1c (%)	6.00 (5.80 to 6.85)	6.60 (6.10 to 7.40)	0.1123
TC (mg/dl)	143 (134 to 170)	159 (145 to 181)	0.1400
HDL (mg/dl)	54.5 (47.0 to 61.0)	59.0 (51.5 to 71.0)	0.1113
LDL (mg/dl)	70.3 (65.5 to 107.9)	83.0 (70.0 to 104.1)	0.4795
TG (mg/dl)	63.0 (41.0 to 88.5)	64.0 (54.0 to 80.0)	0.5838
BMI Z-score	0.52 (-0.03 to 0.76)	0.14 (-0.48 to 0.79)	0.3719
ins/kg (unit/kg)	0.51 (0.33 to 0.71)	0.53 (0.41 to 0.76)	0.5378

linked with type 2 diabetes (T2D) mellitus due to their clinical similarities. The dominant feature of T2D is systemic insulin resistance which results in impaired fasting glucose, impaired insulin tolerance and, finally, hyperglycemia. However, low-grade chronic inflammation and excessive adiposity are both established factors of its pathophysiology. Similarly, patients with psoriasis also present higher insulin resistance than healthy controls [19,20], lower HDL cholesterol concentration with lower cholesterol efflux capacity and more atherogenic NMR profile of LDL [20]. Moreover, a detailed study by Romani et al. proved that adipokines (leptin, lipocalin-2 and retinol-binding protein 4) are linked with psoriatic inflammation and independent of symptomatic treatment, which suggests that adipose tissue is involved in the disease pathogenesis [21]. Finally, the association of these two diseases is supported by epidemiological studies showing that that patients with psoriasis have an increased risk of developing type 2 diabetes [22] and risk of the metabolic syndrome (a pathological cluster of obesity, hypertension, insulin resistance and dyslipidemia that further drive their cardiovascular risk [23]).

In children with psoriasis the prevalence of the metabolic syndrome and its components is also higher than in reference pediatric populations [24]. A closer examination by Tom et al. also revealed that these patients have (statistically near significance) tendency toward higher insulin resistance than matched healthy control group assessed with HOMA IR [25]. Moreover, in this study the psoriasis and control group had similar TC, LDL, HDL and TG concentrations, like in our patients, but the differences appeared in more precise tests. In NMR spectroscopy, psoriatic children had higher concentration of apolipoprotein B and decreased fraction of large HDL. Moreover, the cholesterol efflux capacity of HDL was lower than in controls. This shows that children affected with psoriasis have not only more atherogenic cardiometabolic profile, but that it is consistent with what we see in older psoriatic patients and patients with DM2. This demonstrates that lipid abnormalities and atherogenic tendencies appear discretely in the course of psoriasis and get exacerbated with disease duration.

Contrary to our expectations, children with psoriasis did not demonstrate any significant lipid abnormalities during regular tests 6 months after T1D diagnosis. Still, it is possible that these patients had functional abnormalities of lipoproteins that would need more sophisticated tests to uncover.

Our study suggests that psoriasis-related inflammation, lipid abnormalities and insulin resistance were not abundantly present in children patients at after 6 months of T1D duration. In turn, concomitant psoriasis was associated with milder beginning of T1D. This may be purely coincidental or, on the other hand, the altered phenotype may be an effect of shared genetic background of psoriasis and T1D, which would make our group (or at least a few carefully selected patients) a good target for genetic testing.

Considering the observations in adults, we noted that children with T1D and psoriasis may present an altered clinical course of diabetes. Due to suspected insulin resistance, we expected worse metabolic control, closer clinically to "double diabetes", i.e. type 2 diabetes developing in children with T1D.

However, the study showed that patients with psoriasis had somewhat milder beginning of T1D. At onset, they had higher concentrations of serum C-peptide which corresponded to better endogenous insulin secretion. Moreover, we also found slightly lower levels of HbA1c 6 months after T1D diagnosis than in children without psoriasis. HbA1c is an established surrogate of prolonged glycemic control, corresponding to mean glycaemia from about 3 months prior to testing. The difference between groups was small, but enough to classify more patients with psoriasis as having optimal diabetes control, in contrast to their T1D-only peers, who more often present suboptimal control.

All above-mentioned differences were supported by the fact that 6 month after T1D diagnosis some patients with psoriasis tend to be still in partial remission. This state, otherwise known as "honeymoon period" is defined as low insulin demand coupled with optimal glycemic control [26].The cut-off points for partial remission differ among publications [26,27], but the strict definition by Diabetes Poland modeled on reports by Scholin et al. [26] seems to best identify children with clinical remission.

Honeymoon period – resulting from a recovery of residual insulin secretion – is viewed as a possible therapeutic window for intervention aimed at protecting the remaining β-cells. Its duration varies by patients and applied definitions [27,28]. The fact that patients with concomitant psoriasis tended to remain in remission as late as 6 months after T1D onset, suggests that the intensity of autoimmune β-cells destruction may be lower in their case than in their T1D-only peers. However, the groups had similar frequencies of positive autoantibodies which needs to be clarified by prospective study using a single reference method to compare concentrations of autoantibodies and not only their significant presence.

The shortcoming of this study is our scarce knowledge on clinical course of psoriasis in our study group, including the duration of clinically present psoriasis at T1D onset.

Conclusions

We present the first report on change in the clinical course of T1D with coexisting psoriasis in pediatrics. Children with psoriasis have better endogenous insulin secretion at T1D onset and a tendency for better glycemic control during the first 6 months of T1D duration.

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