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Clinical determinants of the remission phase in children with new-onset type 1 diabetes mellitus in two years of observation

Kliniczne determinanty remisji u dzieci z nowo rozpoznaną cukrzycą typu 1 w dwuletniej obserwacji

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Abstract
Possibilities of prolonging endogenous insulin production during the "remission phase" of type 1 diabetes (T1DM) have been the focus of much interest in recent research.
The aim of the study was to describe the course of clinical remission in children with new-onset type 1 diabetes and to compare the selected markers affecting the presence of partial clinical remission (CR), focusing, among others, on physical activity before/during diagnosis.
Material and methods: We recruited 82 children (aged 10 ±3.72 years) with T1DM. We gathered data regarding the course of the disease (two years of observation), insulin treatment, and laboratory results. Endogenous insulin production was assessed on the basis of C-peptide fasting and prandial level. Remission of diabetes was defined according to actual criteria. Information about physical activity (PA) was obtained by telephone interview.
Results: Patients with no physical activity, in comparison with those with a high level of PA before the diagnosis, had significantly worse parameters of acid-base balance at admission ($p < 0.05$). Patients with a higher PA level in the course of T1DM had significantly lower insulin requirements three months after diagnosis ($p < 0.05$). Patients < 10 years of age presented worse acid-base balance parameters ($p < 0.05$) at admission, lower fasting and postprandial C-peptide concentrations at admission ($p < 0.05$) and after two years of observation ($p = 0.00$), compared to the > 10-year-old group. In a follow-up lower insulin dose on the day of discharge and after 6 and 12 months, and higher postprandial C-peptide concentration was observed in patients with HbA_{1c} below 11.3% (median) at admission compared to the group with HbA_{1c} above 11.3%. Patients with remission at discharge from hospital presented fewer metabolic disturbances at admission ($p < 0.05$) and lower insulin requirements from the date of discharge ($p = 0.00$) to the end of the first year ($p < 0.05$).
Conclusions: Lower insulin demand at discharge from hospital after diagnosis of T1DM in a child is connected with older age, lower HbA_{1c} level, and better clinical condition at admission. Higher PA affects better biochemical parameters at diagnosis of T1DM and lower demand for insulin later. During the first two years of the disease clinical remission may be connected with higher physical activity, but longitudinal studies are still required.
Key words:
clinical remission, diabetes type 1 onset, C-peptide, physical activity.

Streszczenie
Możliwości przedłużenia wydzielania endogennej insuliny w trakcie „miesiąca miodowego" w cukrzycy typu 1 są obecnie szeroko badane.
Cel pracy: Opisanie trwania klinicznej remisji u dzieci z nowo rozpoznaną cukrzycą typu 1, porównanie wybranych czynników mających wpływ na wystąpienie remisji, skupiając się na aktywności fizycznej przed chorobą oraz w jej trakcie.

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Materiał i metody: Grupa badana składała się z 82 dzieci (10 ±3,72 roku) chorych na cukrzycę typu 1. Zebrano i przeanalizowano dane dotyczące czasu trwania choroby (dwuletnia obserwacja), zapotrzebowania na insulinę i wyników laboratoryjnych. Endogenne wydzielanie insuliny określono na podstawie stężeń C-peptydu na czczo oraz 2 godziny po posiłku. Remisję cukrzycy zdefiniowano zgodnie z aktualnymi kryteriami. Informacje na temat aktywności fizycznej uzyskano na podstawie ankiety telefonicznej.
Wyniki: Pacjenci, którzy nie wykazywali aktywności fizycznej w porównaniu z pacjentami z wysokim poziomem aktywności fizycznej przed diagnozą, zostali przyjęci do szpitala z gorszymi wynikami parametrów równowagi kwasowo-zasadowej ($p < 0,05$). Pacjenci wykazujący wysoki poziom aktywności fizycznej w trakcie choroby mieli niższe zapotrzebowanie na insulinę po 3 miesiącach od rozpoznania ($p < 0,05$). Pacjenci poniżej 10. roku życia prezentowali gorsze wyniki parametrów równowagi kwasowo-zasadowej ($p < 0,05$), mniejsze stężenia C-peptydu na czczo oraz 2 godziny po posiłku ($p < 0,05$) przy przyjęciu do szpitala oraz mniejsze stężenie C-peptydu w dwuletniej obserwacji ($p = 0,00$) w porównaniu z pacjentami powyżej 10. roku życia. U pacjentów z poziomem hemoglobiny glikowanej (HbA_{1c}) poniżej 11,3% (mediana) w dniu przyjęcia do szpitala zaobserwowano większe stężenie C-peptydu 2 godziny po posiłku, niższe zapotrzebowanie na insulinę w dniu wypisu oraz po 6 i 12 miesiącach od diagnozy w porównaniu z pacjentami z HbA_{1c} powyżej 11,3%. Pacjenci z remisją w dniu wypisu ze szpitala byli przyjęci do niego w lepszej kondycji, a następnie wykazywali niższe zapotrzebowanie na insulinę przez rok od diagnozy ($p < 0,05$).
Wnioski: Niższe zapotrzebowanie na insulinę w dniu wypisu związane jest z: starszym wiekiem, niższym poziomem HbA_{1c} oraz lepszym stanem klinicznym w dniu przyjęcia do szpitala. Wyższy poziom aktywności fizycznej wpływa na lepsze wyniki parametrów równowagi kwasowo-zasadowej w czasie rozpoznania cukrzycy typu 1 oraz na niższe zapotrzebowanie w trakcie jej trwania. W ciągu dwóch pierwszych lat od diagnozy remisja może być związana z wyższym poziomem aktywności fizycznej, jednakże dalsze badania w większej grupie badanej są konieczne.
Słowa kluczowe:
remisja kliniczna, cukrzyca typu 1, zachorowanie, C-peptyd, aktywność fizyczna.

Introduction

Type 1 diabetes mellitus (T1DM) is characterised by selective and progressive autoimmune destruction of pancreatic beta cells in genetically susceptible individuals [1]. The first symptoms of T1DM usually occur several years after the destruction process has started [2, 3]. The end-stage condition is a lack of endogenous insulin production, resulting in elevated blood glucose levels. Hyperglycaemia is a factor affecting the activation of the immune system, metabolic processes, and escalating oxidative stress [4]. A few decades ago it was believed that total destruction of the beta cells, once started, is inevitable; a belief which was implied by the growing need for insulin [5]. Now we know that some β cells may remain and may still be functional, even after decades of the course of the disease [6, 7]. Effective insulin therapy reduces glucose toxicity and may affect partial recovery of surviving beta cells and increased endogenous insulin production [8, 9]. This may result in partial clinical remission (CR), also known as the honeymoon phenomenon. During the partial clinical remission period the exogenous insulin requirement decreases with proper metabolic control of diabetes and the blood glucose levels are frequently stable and within the normal range. Furthermore, residual endogenous insulin secretion in patients with T1DM is associated with improved long-term glycaemic control, reduced risk of severe hypoglycaemia [10], and reduced risk for chronic microvascular complications in patients who entered partial CR [11]. According to the International Society for Paediatrics and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2014, the partial remission phase is defined as an insulin requirement of < 0.5 units/kg of body weight per day and glycated haemoglobin (HbA_{1c}) < 7%. Recently, insulin dose-adjusted HbA_{1c}, defined as HbA_{1c} (%) + 4 × (insulin dose in units/kg/24 h), has been proposed as a more specific measure of remission [12].

It is important to discover which patients are predisposed to retaining some degree of endocrine function of the pancreas for a long period of time, and if anything can be done to preserve it. Recent studies have shown that appropriate treatment and follow-up during the honeymoon have the potential to enable the prolongation of this period for years, or even to permanently stop the destruction of the remaining ß cells; hence, the renewal of interest on the subject. Moreover, several studies have found a correlation between various factors and the occurrence of CR in T1DM. In children, young age at presentation, ketoacidosis, and low C-peptide concentrations at diagnosis connected with lower BMI reduce the likelihood of a remission phase. Additionally, the factors associated with the presence of CR taken into consideration are: HbA_{1c} and selected antibody levels [13].

Although the beneficial effects of physical activity (PA) in the general population are numerous, many recommendations about PA for patients with T1DM are based on conclusions derived from studies on patients with type 2 diabetes (T2DM) or on healthy individuals. In adult patients, higher level of PA is connected with improved cardiovascular fitness, better bone-health, and enhanced psychological well-being [14, 15]. No study has taken into consideration the impact of physical activity (PA) level on the occurrence of clinical remission in children with T1DM.

The aim of the present study was to describe the course of clinical remission in children with new-onset T1DM, and to compare the selected markers affecting the presence of partial CR, focusing on physical activity level before and during T1DM.

Material and methods

For the study, we recruited 82 patients (aged 10 ±3.71 years) hospitalised in the Department of Paediatrics, Endocrinology, and Diabetology with Cardiology Division of the Medical University of Bialystok between 2015 and 2018 due to diagnosed T1DM, according to the ISPAD criteria [16]. The disease was diagnosed in accordance with the guidelines, by clinical manifestation, high serum glucose, and the presence of autoantibodies characteristic of type 1 diabetes mellitus (ICA, IAA, and anti-GAD) [16].

All patients were treated with insulin (multiple daily injections of insulin or continuous subcutaneous insulin infusion). Partial CR during the course of diabetes type 1 was defined as an insulin requirement < 0.5 units/kg of body weight and below 7%. For the purposes of the study, partial CR at the day of discharge from hospital was defined as low insulin demand (< 0.5 units/kg of body weight). Due to short time from diagnosis the HbA_{1c} value could not be taken as a criterion. The frequency of partial CR was evaluated at the: 3rd, 6th, 12th, and 24th month after diagnosis. At diagnosis of T1DM the analysed parameters were: blood sugar level at admission (mg/dl), BMI-SDS, recent weight loss (kg), HbA_{1c} (%), pH, HCO3, BE, fasting C-peptide and postprandial C-peptide concentrations (ng/ml), insulin dose (IU/kg), and presence of the following antibodies: GADA, IA2A, and ICA. Our analysis included also parameters as follows: insulin dose (IU/kg), HbA_{1c} (%), age (years), fasting C-peptide (ng/ml), and BMI-SDS in the selected time points. We also analysed the level of physical activity before and during T1DM. Based telephone conversations with parents, the study group was divided into three groups as follows: no physical activity, only PE (physical education), and PE and additional sport classes.

The insulin dose was assessed as daily insulin dose per kilograms of body weight (IU/kg). HbA_{1c} was determined by high-performance liquid chromatography (HPLC) using the Bio-Rad VARIANT™ HbA_{1c} Program (Bio-Rad Laboratories, Inc., Hercules, CA, USA), with its values represented as percentages. Reference values of HbA_{1c} for healthy people ranged from 4.7% to 5.7% [17]. The biological material for the study was venous blood collected from fasting patients. Next, plasma was obtained from the samples, which was used to determine the C-peptide concentration. C-peptide levels were estimated by applying the commercially available electrochemiluminescence method (ECLIA) (Roche Diagnostics GmbH, Penzberg, Germany). Fasting C-peptide levels in healthy individuals ranged from 0.9 to 4.0 ng/ml, and the detection limit was assessed as 0.01 ng/ml for the assay.

Basic physical examination was performed. All children underwent physical examination, and height and weight were taken in a standard way using Harpenden stadiometer and digital scale (Seca, Germany). BMI (body mass index)-SDS (standard deviation score of BMI, according to the formula: SDS-BMI= [BMI current – BMI 50 centile]/0.5 [BMI 50 centile – BMI 3rd centile]) was calculated with standard formulas, using the results of the OLAF study of Polish children [18].

Statistical analysis

Statistical analysis was performed using Statistica 12.00 software (StatSoft, Kraków, Poland). The Kolmogorov-Smirnov test of normality was used to test the distribution of variables. For normally distributed variables, the unpaired Student t-test was used, and for non-normally distributed variables the Mann-Whitney U-test was used to compare the differences between the two groups. Relations between variables of interest were assessed by Pearson's correlation coefficient for parametric and Spearman's rank coefficient for nonparametric data. All data are expressed as either mean ± SD or median (interquartile range). Statistical significance was determined at the level $p < 0.05$. The approval of the Ethical Committee in the Medical University of Bialystok was obtained. Both parents/legal guardians and children gave their written, informed consent.

Results

The general characteristics of the study group are presented in Table 1. Most often the ISPAD criteria of remission were fulfilled within the 3rd and 6th month after diagnosis: 60% and 53% followed by 27% in the 12th month and 29% after two years of follow-up. No cases of complete CR were observed. Comparing children without physical activity with those who attended additional sport classes before diagnosis, it can be seen that they had worse metabolic parameters, such as pH, HCO3, and BE ($p < 0.05$) (Table 2) and higher HbA_{1c} ($p = 0.046$) after one year of follow-up. Children who, during the course of T1DM, participated in additional sport classes had higher postprandial C-peptide concentrations at admission than children who only participated in PE ($p = 0.049$). They also had lower demand for insulin after three months ($p = 0.011$) and after 6, 12, and 24 months (without statistical significance) (Fig. 1). Children who were more than 10 years old at diagnosis were admitted with better biochemical parameters (pH, HCO3, BE, HbA_{1c}, $p < 0.05$), had higher fasting C-peptide concentration ($p = 0.0006$), higher postprandial C-peptide concentration ($p = 0.0004$) (Fig. 2), and higher C-peptide concentration at two-year observation ($p = 0.0004$) than children who were less than 10 years old when diagnosed (Table 3). We obtained the same results when we compared children at age less than 10 years with children older than 15 years. Children older than 15 years had higher fasting C-peptide concentration (0.49 ±0.28 vs. 0.68 ±0.25 ng/ml, $p = 0.044$), postprandial C-peptide concentration (1.12 ±0.5 vs. 2.17 ±1.5 ng/ml, $p = 0.001$) at diagnosis, and higher fasting C-peptide concentration at two-year observation (0.25 ±0.31 vs. 0.78 ±0.17 ng/ml, $p = 0.00$) than children below 10 years old. There were no significant differences in C-peptide concentrations at diagnosis in the group of children aged 11-14 and ≥ 15 years. The children in whom diagnosis of T1DM was accompanied by acidosis and worse condition had lower fasting C-peptide concentration ($p = 0.02$), lower postprandial C-peptide concentration ($p = 0.018$), and also higher demand for insulin at the day of

discharge ($p = 0.042$) and after 6 months (0.005) as well as higher HbA_{1c} level after three months (0.026) than children who were admitted without acidosis (Table 4). Children with higher level (above median = 11.3%) at admission had significantly higher insulin requirement at the day of discharge ($p = 0.003$) and three months after diagnosis ($p = 0.015$). We observed also a negative correlation between the postprandial C-peptide level and HbA_{1c} at diabetes diagnosis ($p = 0.032$).

Patients with remission at discharge from hospital presented fewer metabolic disturbances at admission (pH, HCO3, BE, $p < 0.05$) and lower insulin requirements from the date of discharge ($p = 0.00$) to the end of the first year ($p < 0.05$) (Table 5).

Table I. General characteristics of the study group

	Mean value ± SD	Minimum value	Maximum value
Age at time of diagnosis (years)	10 ±3.72	1.5	18
HbA_{1c} at time of diagnosis (%)	11.70 ±2.52	6	20
Weight loss (kg)	2.52 ±2.65	0	10
SDS BMI at time of diagnosis	–0.23 ±1.25	–2.55	2.95
pH value at admission	7.34 ±0.1	7.04	7.50
HCO_3 value at admission	16.06 ±6.21	3.3	24.90
BE value at the admission	–8.48 ±7.2	–26.60	0.30
Fasting C-peptide concentration	0.62 ±0.37	0.04	1.85
Postprandial C-peptide concentration (after 2 h)	1.56 ±1.13	0.33	6.25
Insulin dose at the discharge (IU/kg)	0.57 ±0.25	0	1.23
GADA (U/ml)	484 ±1279	0.54	10581
IA-2A (U/ml)	540 ±786	0	3626
ICA (U/ml)	42 ±82	0	640

HbA_{1c} – glycated haemoglobin; BE – base excess; HCO_3 – bicarbonate; ICA – islet cell antibodies; GADA – glutamic acid decarboxylase antibodies; IA-2A – tyrosine phosphatase antibodies

Table II. Comparison of biochemical blood parameters at admission to hospital of patients with no physical activity and in patients with extra physical activity before diagnosis of T1DM

	Patients with no physical activity before T1DM	Patients with extra physical activity before T1DM	*p* value
pH	7.20 ±0.12	7.20 ±0.12	0.00
HCO_3	9.70 ±8.77	9.70 ±8.77	0.03
BE	–17.56 ±10.63	–17.56 ±10.63	0.01
HbA_{1c} (%)	12.17 ±3.42	12.17 ±3.42	0.74
Fasting C-peptide concentration (ng/ml)	0.53 ±0.43	0.53 ±0.43	0.46

Data represented as mean ± standard deviation

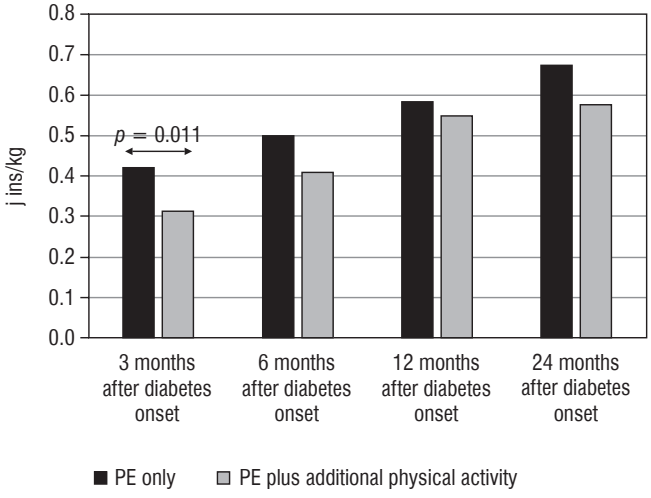

Figure 1. Demand for insulin in ins/kg body mass in children compared in accordance due to physical activity during course of the diabetes (PE – only physical education lessons and PE plus additional physical acitivity) after 3 months ($p = 0.011$) and after 6, 12, 24 months (without statistical significance) of diabetes onset

In our study we observed a positive correlation between BMI-SDS at diabetes diagnosis and fasting C-peptide concentration ($p = 0.025$). We compared patients with BMI-SDS higher than median BMI-SDS (–0.3) with those who had BMI-SDS lower than median BMI-SDS. Our results showed that the first group presented significantly higher fasting ($p = 0.003$) and postprandial C-peptide concentrations ($p = 0.03$) as well as lower insulin demand at the day of discharge ($p = 0.01$), after three months ($p = 0.001$), and 6 months after diagnosis ($p = 0.03$), and higher C-peptide in 2-year observation ($p = 0.01$) (Table 6).

Discussion

The prevalence of the remission phase in T1DM detected in different studies varies widely (30-80%), which partly reflects the use of different definitions (as mentioned above) [19, 20]. On average, the phase tends to appear approximately three months after the beginning of the insulin therapy. After that, the remission rate declines with the duration of the disease: 0-20% at 6 months and only 0-10% at 12 months [21]. In our group, at discharge from hospital 42% of patients had insulin demand < 0.5 U/kg of body weight and presented fewer metabolic disturbances at admission (HCO, BE) and lower insulin

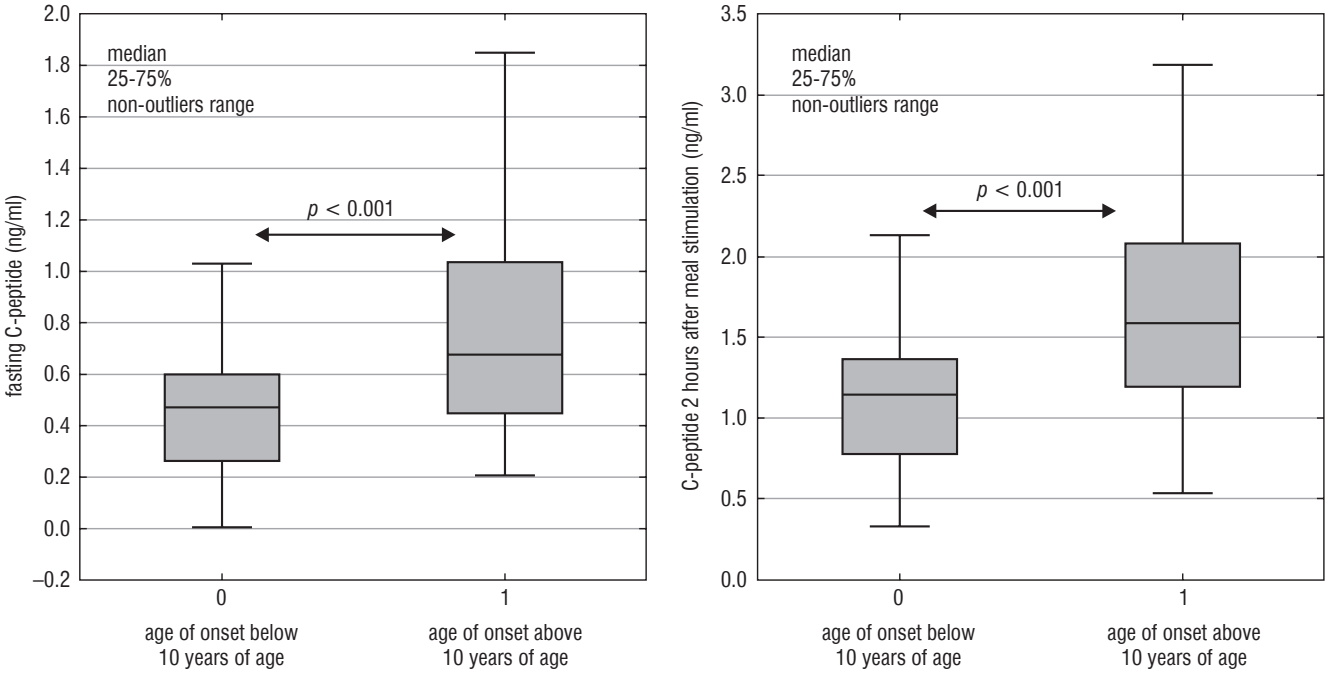

Figure 2. Fasting and postprandial C-peptide concentrations in patients at diagnosis of T1D divided into groups: below and above 10 years of age

Table III. Comparison between patients under 10 years of age and patients over 10 years at the time of type 1 diabetes diagnosis

	Patients' age < 10 years when diagnosed	Patients' age > 10 years when diagnosed	*p* value
SDS BMI at time of diagnosis	0.007 ±1.4	–0.455 ±1.1	0.1
HbA_{1c} at time of diagnosis (%)	11.07 ±2	12.25 ±2.82	0.03
pH value at admission	7.31 ±0.11	7.37 ±0.07	0.01
HCO_3 value at admission	14.05 ±6.7	17.88 ±5.1	0.00
BE value at admission	–11 ±7.9	–6 ±5.7	0.00
Fasting C-peptide concentration (ng/ml)	0.46 ±0.2	0.75 ±0.4	0.00
Postprandial C-peptide concentration after 2 h (ng/ml)	1.07 ±0.5	1.98 ±1.3	0.00
Insulin dose at discharge (IU/kg)	0.53 ±0.3	0.61 ±0.2	0.15
HbA_{1c} after 3 months (%)	6.67 ±0.7	6.64 ±0.7	0.85
Insulin dose after 3 months (IU/kg)	0.36 ±0.2	0.38 ±0.2	0.63
HbA_{1c} after 6 months (%)	6.47 ±0.6	6.48 ±0.8	0.97
Insulin dose after 6 months (IU/kg)	0.49 ±0.2	0.43 ±0.2	0.32
HbA_{1c} after 12 months (%)	6.55 ±0.9	6.95 ±1.1	0.1
Insulin dose after 12 months (IU/kg)	0.56 ±0.2	0.58 ±0.2	0.69
HbA_{1c} after 24 months (%)	6.67 ±0.7	6.96 ±1.3	0.38
Insulin dose after 24 months (IU/kg)	0.60 ±0.3	0.69 ±0.3	0.38
HbA_{1c} at 2-year observation (%)	6.67 ±0.6	6.70 ±0.8	0.39
C-peptide concentration in observation (ng/ml)	0.22 ±0.3	0.74 ±0.6	0.00

Data represented as mean ± standard deviation

requirements from the date of discharge ($p = 0.00$) to the end of the first year. Three months after diagnosis partial remission was observed in 60% of patients, after 6 months in 53% of individuals, after one year in 27% of them, and in 29% of them after 2 years of follow-up. The fact that there were no case of complete remission in the study group confirms that it occurs as rarely as mentioned in another study [22]. In another Polish study CR was observed in 61.83% (115/186) of patients, and often the criteria of remission were fulfilled within the 3rd and 6th month after diagnosis: 36.56% (68/186) and 39.25% (73/186), followed by 24.19%, 13.44%, and 12.37% in the 12th, 18th, and 24th months, respectively [23].

A physically active lifestyle is important in the prevention and treatment of many chronic diseases and conditions. The independent effect of physical activity in diabetes prevention is not known, but its role as a key component of lifestyle intervention has been widely described [24]. In children with T1DM, this level of physical activity can benefit glycaemic control, insulin sensitivity, protect against cardiovascular disease, and improve body composition, quality of life, and lifelong health [25]. On the other hand, due to an impaired blood glucose regulatory capability, patients with T1DM are at increased risk of adverse response to exercise when compared with healthy individuals. However, the risks of physical activity can be largely controlled with careful screening, pre-exercise preparation, and appropriate exercise prescription [26]. As mentioned, patients with T1DM who are physically more active have a lower overall risk of cardiovascular events than their sedentary counterparts; therefore, this long-term benefit more than compensates for the minor increase in acute risk when physical activity programs are started [27]. Furthermore, current evidence suggests that the acute risks of physical activity-related adverse events are

Table IV. Comparison between patients who were admitted to hospital with/without acidosis and diagnosed with type 1 diabetes

	Patients with acidosis	Patients without acidosis	*p* value
Age (years)	8.26 ±3.2	10.7 ±3.7	0.01
pH value at admission	7.21 ±0.07	7.39 ±0.05	0.00
HCO_3 value at admission	7.69 ±2.95	19.32 ±3.46	0.00
BE value at admission	–18.4 ±4.13	–4.61 ±3.41	0.00
HbA_{1c} at time of diagnosis (%)	11.77 ±1.7	11.66 ±2.8	0.87
Fasting C-peptide concentration at time of diagnosis (ng/ml)	0.44 ±0.19	0.67 ±0.4	0.02
Postprandial C-peptide concentration after 2 h (ng/ml) at time of diagnosis	0.98 ±0.5	1.73 ±1.2	0.02
Insulin dose at discharge (IU/kg)	0.66 ±0.23	0.54 ±0.25	0.04
HbA_{1c} after 3 months (%)	6.94 ±0.86	6.54 ±0.62	0.02
Insulin dose after 3 months (IU/kg)	0.4 ±0.18	0.36 ±0.17	0.45
HbA_{1c} after 6 months (%)	6.49 ±0.85	6.44 ±0.62	0.75
Insulin dose after 6 months (IU/kg)	0.58 ±0.27	0.41 ±0.2	0.01
HbA_{1c} after 12 months (%)	6.77 ±0.1	6.73 ±1	0.88
Insulin dose after 12 months (IU/kg)	0.6 ±0.2	0.55 ±0.2	0.37
HbA_{1c} after 24 months (%)	6.91 ±1.22	6.78 ±0.97	0.73
Insulin dose after 24 months (IU/kg)	0.7 ±0.27	0.63 ±0.27	0.48
HbA_{1c} at 2-year observation (%)	6.74 ±0.98	6.59 ±1.22	0.37
C-peptide concentration in observation (ng/ml)	0.36 ±0.36	0.51 ±0.57	0.36

Data represented as mean ± standard deviation

low [26]. However, there are still no data on the impact of physical activity level on the occurrence of clinical remission in paediatric patients with type 1 diabetes. In our study we evaluated the level of physical activity before diagnosis and during the course of diabetes based on retrospectively collected data. Our results showed that children who participated in additional sports classes during the course of T1DM had higher postprandial C-peptide concentration than children who only took part in physical education classes at school. They also had significantly lower demand for insulin after three months as well as after 6, 12, and 24 months (but without statistical significance). When we compared children who undertook no physical activity with those who attended additional sports classes before diagnosis, the results indicated that they had worse metabolic parameters at admission to hospital (pH, HCO_3, BE) and higher HbA_{1c} after one year of follow-up. The results of our study suggest that doing exercise around the time of T1DM diagnosis could have an impact on better metabolic status of patients at diabetes diagnosis and extend the "honeymoon" period of low insulin requirement.

The preservation of residual β-cell function, measured by C-peptide level, is clinically important because it is associated with reduced blood glucose fluctuations and has a protective effect on both acute and long-term diabetes complications [29]. In our study children aged over 10 years at time of diagnosis had higher fasting and postprandial C-peptide levels as well as higher C-peptide concentration after two years of observation compared to subjects younger than 10 years. Our

Table V. Comparison between patients with/without partial remission at the day of discharge from hospital

	Patients with remission	Patients without remission	*p* value
Age (years)	9 ±3.5	10 ±3.7	0.2
SDS BMI at time of diagnosis	0.25 ±1.1	–0.58 ±1.2	0.00
pH value at admission	7.37 ±0.1	7.32± 0.1	0.02
HCO_3 value at admission	18.2 ±5.6	14.4 ±6.3	0.00
BE value at admission	–6.2 ±7.1	–10.3 ±6.7	0.00
HbA_{1c} at time of diagnosis (%)	10.94 ±2.63	12.36 ±2.2	0.00
Fasting C-peptide concentration at time of diagnosis (ng/ml)	0.6 ±0.3	0.63 ±0.4	0.77
Postprandial C-peptide concentration after 2 h (ng/ml) at time of diagnosis	1.68 ±1.1	1.36 ±0.9	0.17
Insulin dose at discharge (IU/kg)	0.34 ±0.1	0.74 ±0.2	0.00
HbA_{1c} after 3 months (%)	6.57 ±0.8	6.72 ±0.7	0.36
Insulin dose after 3 months (IU/kg)	0.25 ±0.12	0.46 ±0.15	0.00
HbA_{1c} after 6 months (%)	6.5 ±0.66	6.45 ±0.72	0.78
Insulin dose after 6 months (IU/kg)	0.35 ±0.16	0.54 ±0.24	0.00
HbA_{1c} after 12 months (%)	6.58 ±0.89	6.87 ±1.1	0.22
Insulin dose after 12 months (IU/kg)	0.5 ±0.18	0.63 ±0.2	0.01
HbA_{1c} after 24 months (%)	6.8 ±0.9	6.83 ±1.1	0.92
Insulin dose after 24 months (IU/kg)	0.58 ±0.3	0.7 ±0.25	0.22
HbA_{1c} at 2-year observation (%)	6.69 ±0.57	6.56 ±0.74	0.4
C-peptide concentration in observation (ng/ml)	0.34 ±0.34	0.5 ±0.6	0.3

Data represented as mean ± standard deviation

observation was consistent with the results of Szypowska *et al.*, who found also that children > 10 years old had higher fasting C-peptide concentration, and moreover their findings were based on a study group with 1098 Polish children [30]. The results of a study performed by Samuelsson *et al.* also confirmed our findings [31]. In general, prepubertal children have lower measurable C-peptide at the time of diagnosis than older individuals. While normative data in younger healthy children is not readily available, most consider this lower value to reflect that adult β cell mass is not reached until early adolescence [32]. Our, as well as the other mentioned authors', observations may suggest a rapid and more extensive destruction of β cells or a reduced capacity to regenerate β cells in very young children.

We observed also a negative correlation between the postprandial C-peptide level and HbA_{1c} at diabetes diagnosis. In the mentioned study performed by Szypowska *et al.* a negative correlation was noted between the fasting C-peptide concentration and HbA_{1c} at diabetes diagnosis [30]. In line with other studies, we noted statistically lower fasting (and postprandial) C-peptide levels in children with diabetic ketoacidosis compared to those without [30, 33]. When diagnosed with diabetes, if the patient presents with severe ketoacidosis, it seems to negatively impact the onset and duration of remission (49.5% of the patients without DKA had partial remission compared to only 18.3% of patients with DKA) [34, 35]. This fact is in accordance with other studies from the USA and Kuwait, which also denoted this cor-

Table VI. Comparison between patients with BMI-SDS higher than median BMI-SDS (–0.3) and those who had BMI-SDS lower than median BMI-SDS (–0.3)

	Patients with BMI-SDS above –0.3	Patients with BMI-SDS below –0.3	*p* value
Age (years)	10 ±3.5	10 ±3.9	0.6
pH value at admission	7.34 ±0.1	7.34 ±0.08	0.77
HCO_3 value at admission	16.4 ±6.73	15.8 ±5.8	0.64
BE value at admission	–8.4 ±7.9	–8.6 ±6.6	0.89
HbA_{1c} at time of diagnosis (%)	11.27 ±2.6	12.1 ±2.4	0.16
Fasting C-peptide concentration at time of diagnosis (ng/ml)	0.75 ±0.4	0.5 ±0.3	0.00
Postprandial C-peptide concentration after 2 h (ng/ml) at time of diagnosis	1.88 ±0.43	1.29 ±0.28	0.03
Insulin dose at discharge (IU/kg)	0.5 ±0.22	0.64 ±0.26	0.01
HbA_{1c} after 3 months (%)	6.75 ±0.7	6.57 ±0.7	0.3
Insulin dose after 3 months (IU/kg)	0.3 ±0.2	0.43 ±0.1	0.00
HbA_{1c} after 6 months (%)	6.44 ±0.67	6.50 ±0.72	0.75
Insulin dose after 6 months (IU/kg)	0.4 ±0.2	0.52 ±0.2	0.03
HbA_{1c} after 12 months (%)	6.8 ±1	6.7 ±1	0.64
Insulin dose after 12 months (IU/kg)	0.55 ±0.22	0.59 ±0.2	0.52
HbA_{1c} after 24 months (%)	6.9 ±1	6.7 ±1.2	0.56
Insulin dose after 24 months (IU/kg)	0.63 ±0.3	0.68 ±0.3	0.65
HbA_{1c} at 2-year observation (%)	6.68 ±0.64	6.6 ±0.7	0.6
C-peptide concentration in observation (ng/ml)	0.6 ±0.6	0.3 ±0.3	0.1

Data represented as mean ± standard deviation

relation [13, 34]. Increased awareness of T1DM symptoms as well as improved screening and diagnostic tools are important to preserve C-peptide levels.

In our study we observed a positive correlation between BMI-SDS at diabetes diagnosis and fasting and postprandial C-peptide concentrations at the same time. We compared patients with BMI-SDS higher than median BMI-SDS (–0.3) with those who had BMI-SDS lower than median BMI-SDS. Our results showed that the first group presented significantly higher fasting and postprandial C-peptide concentrations as well as lower insulin demand for 6 months after diagnosis. Yu *et al.* showed that the preserved C-peptide level increased 5-fold in overweight or obese (compared to underweight) children [36]. Redondo *et al.* observed that preserved C-peptide increased 2.4-fold and 4.1-fold in overweight and obese children, respectively, compared to lean children [37]. Moreover, Sosenko *et al.* also noted that C-peptide measures are strongly and independently related to BMI-SDS and age at, and soon after, the diagnosis of T1DM [38]. Pyziak *et al.* observed in their study an association between higher BMI-SDS and partial CR occurrence. The results seem to suggest that obesity/being overweight or having smaller loss of body mass in patients at T1DM diagnosis may predispose to further development of partial CR, and it was observed even in the youngest children below five years of age [23]. Because hyperglycaemia occurs when the amount of insulin secretion is unable to meet insulin demand, an insulin-resistant individual will

present with hyperglycaemia with more residual insulin secretion than someone who is insulin sensitive. This is probably the explanation for those with higher body mass index presenting with higher C-peptide levels at the time of diagnosis [32]. However, the impact of BMI on the rate of C-peptide concentration decline during the course of diabetes type 1 remains unknown.

Conclusions

Clinical remission after onset of T1DM in children is connected with older age, lower HbA_{1c} level, higher body mass, and better clinical condition at the time of disease recognition. Higher PA affects better biochemical parameters at diagnosis of T1DM, and lower insulin demand with higher C-peptide level during the course of diabetes. Defining the factors determining the occurrence of CR is very important, not only for the present but also for future paediatric patients with T1DM. The presence of the honeymoon phenomenon can, however, give benefits, including the search for novel therapeutic options to prolong the period of CR in children with newly diagnosed T1DM.

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