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Оптимизация настроек инсулиновых помп у детей и подростков с сахарным диабетом 1 типа с учетом возрастных особенностей

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Цель. *Выявить особенности суточных колебаний потребности в инсулине и чувствительности к инсулину у детей и подростков с сахарным диабетом 1 типа (СД1), получающих интенсифицированную инсулинотерапию путем постоянной подкожной инфузии инсулина (ППИИ), а также закономерностей их изменения в различные возрастные периоды для оптимизации настроек инсулиновой помпы.*

Материалы и методы. *В исследование вошли 138 детей и подростков с СД1 в возрасте 1–18 лет, получающих интенсифицированную инсулинотерапию путем ППИИ. Все пациенты были разделены на 3 возрастные группы: дошкольники младше 6 лет (n=23), дети до пубертата от 6 до 12 лет (n=39), подростки от 12 до 18 лет (n=76). В каждой группе проанализированы схемы проводимой инсулинотерапии, в том числе среднесуточная доза инсулина (СДИ), соотношение суточной дозы инсулина, вводимого в базальном и болюсном режиме, профили введения инсулина в базальном режиме за сутки, углеводные коэффициенты (УК), факторы чувствительности к инсулину (ФЧИ).*

Результаты. *В ходе исследования обнаружены возрастные особенности изменения потребности в инсулине, вводимом в базальном режиме и болюсно в течение суток. Маленьким детям требуется более высокая скорость инфузии инсулина в базальном режиме в вечерние часы и в первую половину ночи, а минимальная – днем. Детям старшего возраста и подросткам для достижения индивидуальных целевых показателей гликемии требуется более высокая скорость инфузии инсулина в базальном режиме в ранние утренние часы. Также во всех возрастных группах обнаружена зависимость значений УК и ФЧИ от времени суток.*

Заключение. *СДИ, соотношение дозы вводимого в базальном режиме и болюсно инсулина, а также циркадный профиль изменения потребности в инсулине и чувствительности к инсулину существенно зависят от возраста. Полученные в ходе исследования коэффициенты для расчета доз болюсов инсулина значимо отличаются от значений, получаемых с помощью наиболее известных формул. Для индивидуальной настройки инсулиновой помпы с учетом возрастных особенностей используемые формулы для расчета показателей следует модифицировать путем введения в них поправочных коэффициентов.*

Ключевые слова: *сахарный диабет; помповая инсулинотерапия; постоянная подкожная инфузия инсулина; калькулятор болюсов; углеводный коэффициент; фактор чувствительности к инсулину, базальный режим*

Age-adjustment of insulin pump settings in children and adolescents with type 1 diabetes mellitus

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Aim. *This study was aimed at investigation of daily glycemic variations in children and adolescents with type 1 diabetes mellitus (T1DM) on continuous subcutaneous insulin infusion (CSII) in order to define in greater detail the correlation of said parameters with periods of age to the end of improving current recommendations for pump settings adjustment.*

Materials and Methods. *138 children and adolescents aged 1–18 years on CSII therapy took part in this study. Patients were subdivided into three groups according to their age: preschool children (n=23), prepubertal children aged <12 years (n=39) and teenagers up to 18 years old (n=76). CSII regimens were analyzed in every group, including average daily insulin dose, basal-to-bolus ratio, daily basal profiles, carbohydrate ratio (CR) and insulin sensitivity factor (ISF).*

Results. *Daily requirement for both basal and bolus insulin does differ between ages. Youngest children require higher basal infusion rate during evening hours and first half of the nighttime while demonstrating least requirement at daytime. Instead, prepubertal children and adolescents require higher basal infusion rate during early morning hours. We also show CR and ISF to be dependent of daytime in all studied age grades.*

Conclusion. *Basal-to-bolus ratio along with circadian variability in requirement for insulin are clearly governed by patient's age. Importantly, the ratios for bolus calculations, developed from our data, significantly differ from those provided by popular formulas, suggesting the latter be modified into taking regard of the age grade for proper individual adjustment of pump settings.*

Keywords: *diabetes mellitus; insulin pump therapy; CSII; bolus wizard; carbohydrate ratio; insulin sensitivity factor; basal profile*

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Abbreviations

- T1D – type 1 diabetes mellitus
- CSII – continuous subcutaneous insulin infusion
- MDI – multiple daily injection
- CarbF – carbohydrate factor
- ISF – insulin sensitivity factor
- IU/h – insulin rate in basal regimen
- BC – bolus calculator
- TDD – total daily dose of insulin
- Me – mean values

Background

Insulin pump therapy for the treatment of type 1 diabetes (T1D), especially in children and adolescents in recent years have become much more widely used in all countries, including Russia [1–3]. Many studies have shown that continuous subcutaneous insulin infusion (CSII) in the pediatric population is a safe and effective treatment option in T1D [2, 4, 5], providing better glycemic control compared with multiple daily injection (MDI) regimen and a significant reduction frequency of hypoglycemia episodes [2, 6–8]. Benefits of insulin pump therapy were proved in assessing quality of life in T1D children and adolescents [9]. In general, CSII is an effective and safe treatment option in T1D children and adolescents; only a small proportion of patients refuses from it, continuing MDI insulin therapy after 6–12 months of CSII regimen) [10].

However, CSII is associated with a significant information burden on the patient (his family), and expects endocrinologist to have certain experience and skills. In this regard, success CSII implementation in clinical practice [11] requires effective algorithms of conducting T1D patients treatment with insulin pump therapy including all possible stages, from the moment of patient selection to contraindications to CSII regimen.

Such algorithms should include recommendations for individualized insulin pump settings. Thus at different ages insulin requirements and insulin sensitivity may greatly vary not only for 24 hours, but at different times during the day [12, 13]. Thus, recommendations for initial insulin pump settings when transferring T1D patients to CSII, and when adjusting insulin pump settings in patients already using CSII, should be individualized according to age.

Patient's age is almost ignored in international clinical practice guidelines for the selection of initial insulin pump settings and their subsequent adjustment. In the most common formulas of basal insulin regimen estimation, and in carbohydrate factors (CarbF) and insulin sensitivity factors (ISF) determination, patient's age is only indirectly taken into account – via weight.

Basal insulin regimen

Several methods to determine insulin rate in basal regimen when transferring patients from MDI to CSII were proposed [14]. However, recommended formulas allow to estimate only average insulin rate in basal regimen (IU/h). Thus, in most cases during the first few days (before adjustment of initial settings) after transfer to CSII, the patient receives basal insulin with equal rate at different time of day. Only in few cases, when transferring patients to CSII an individual "floating" profile of basal insulin with different infusion rates at different times of day is set. Most often, this "individual" profile is programmed based on the identified patterns of glycemic changes in MDI regimen. This is not quite correct considering differences between CSII and MDI [15].

Individual "floating" profile of basal insulin is rare programmed when transferring patients to CSII taking into account age, body weight and daily insulin requirements. The algorithm described by Renner R. et al. in the 1980's [16, 17] and confirmed in the large clinical studies in 2004–2011 [18] is used for this purpose.

Many patients do not need precise adjustment of individual "floating" profile of basal insulin at the time of transfer to the insulin pump, because in 1–3 days the initial settings are changed according to results of "starvation tests" [12, 19]. However, a full "verification of the basal profile" in the pediatric population presents certain difficulties, especially in young children (test includes carbohydrates elimination, extraordinary physical activity, insulin boluses, as well as hourly blood glucose control for 6–10 hours at different day times within a few days). For these patients algorithm of individualized insulin pump settings allowing on the basis of several external parameters (age, body weight, average daily dose of insulin, glycemic control, etc.) to tailor basal insulin profile at CSII initiation, is particularly important.

Insulin boluses

Most of the modern insulin pumps are equipped with insulin doses calculator, that allows to get the best glycemic control results compared with mental calculates [20]. If insulin pump has no bolus calculator (BC), the patient may use a similar program on his/her phone or smartphone. The coefficients for BC programming when transferring patients to CSII are calculated either with standard formulas ("2000 rule", "2.8 rule", etc. [21–24]), or based on the total daily insulin dose (TDD), or with factors used during MDI.

TDD is an essential measure, the base for individual insulin pump adjustments for basal and bolus insulin calculation. Various formulas to determine the individual BC settings (CarbF and ISF) on the basis of TDD were proposed. The first formula for ISF calculating was proposed in the mid 1980's. This formula, called the "1500 rule," was based on the clinical experience with recombinant human short-acting insulin.

"1500 rule":
ISF [mg/dL/IU] = 1500 / TDD

In 1994, Walsh and Roberts introduced a similar CarbF formula for CSII and MDI [24]. This "450 rule" was based on clinical experience with patients using recombinant human short-acting insulin.

"450 rule":
CarbF [g/IU] = 450 / TDD

Modifications of both formulas have been introduced over the years based on clinical experience with genetically engineered ultra-short-acting insulin analogue: "1800 rule" and "2000 rule" (for children) for ISF; "500 rule" and "300 rule" (for children) for CarbF. Davidson and colleagues were the first to publish a clinical study of pump settings among 167 well-controlled pump diabetic patients in 2003 [22, 23]. Mean daily dose used for basal delivery in this study was 48% of the TDD, also new formula for the CarbF and ISF were derived:

"2.8 rule":
CarbF [g/IU] = (2.8 × weight(lbs)) / TDD

"1700 rule":
ISF [mg/dL/IU] = 1717 / TDD

Considering potential limitations in deriving these formulas (coefficients found without considering whether the pump's dose recommendations were followed, TDD was determined 7 days prior to the visit when HbA_{1c} level was below 7%, all subjects lived in a single geographic location, and the constants were derived using data that clearly had non-Gaussian distributions), Walsh et al. analyzed anonymous settings of 1020 pumps in different USA regions and derived new formulas [21]:

"2.6 rule":
CarbF [g/IU] = (2.6 × weight(lbs)) / TDD
= (5.7 × weight(kg)) / TDD
CarbF [IU/CU] = (a × TDD) / (5.7 × weight(kg))
= (1.75* × TDD) / weight(kg))
*where a (carbohydrates in 1 CU) = 10 g

"2000 rule":
ISF [mg/dL/IU] = 2000 / TDD
ISF [mmol/l/IU] = 2000 / (18 × TDD)
= 111.1 × TDD

The effectiveness of these formulas is currently the most validated as they were obtained in a large amount of material with meeting appropriate methodological criteria and statistical methods. However, age features were not considered, and the resulting formulas did not include age. Adjustment of these coefficients at different times of day is performed based on results of blood glucose self-monitoring.

Purpose and objectives of the study

the purpose of this study was to determine circadian features of insulin requirements (determined by basal and bolus insulin delivery) in T1D children and adolescents, receiving intensive insulin therapy via CSII, as well as patterns of their change at different ages to optimize insulin pump settings.

Materials and methods

the study included 138 T1D children and adolescents receiving intensive basis-bolus insulin therapy via CSII, and treated in Federal State Institution "Endocrinology Research Centre". All patients were stratified to three age groups:

- group 1 – preschool children under 6 years old (n=23);
- group 2 – prepubertal children aged 6 – 12 years (n=39);
- group 3 – adolescents 12 – 18 years old (n=76).

All subjects received genetically engineered insulin analogs and used various models of pumps (Medtronic Paradigm MMT-712, MMT-722, MMT-754, Accu-Chek Spirit, and Accu-Chek Spirit Combo). The main characteristics of evaluated groups are presented in Table. 1.

The study analysis of the insulin pumps at the time of discharge with achievement of individual glycemic control targets: B TDD, ratio of daily basal and bolus insulin, daily basal insulin profiles, CarbF and ISF.

To compare with actual factors (i.e., used by patients), CarbF and ISF were calculated according to following formulas (hereinafter "estimated") [21]:

- "2.6 rule" — CarbF [IU/CU] = (1,75 × TDD) / weight(kg);
- "2000 rule" — ISF [mmol/l/IU] = 2000 / (18 × TDD).

Also, actual constants were calculated for these formulas based on average daily CarbF and ISF.

Results

HbA_{1c} was significantly higher in the second and third age groups compared with first ($p < 0.05$). TDD, circadian features of insulin requirements in terms of patient body weight (TDD/kg), as well as dose of basal insulin increased with increasing patient age. As the age of the patient increased, proportion of the basal insulin dose in the TDD escalated (See Table 1).

Circadian profile of basal insulin requirements профиль изменения потребности во вводимом в базальном режиме инсулине significantly varied in patients of different age groups (Figure 1).

- Patients in the first age group required the highest basal insulin rate delivery in the first half of the night from 00:00 to 03:00, with the lowest rate of insulin delivery in the afternoon from 10:00 to 12:00.
- Children in the second age group were characterized by biphasic profile of basal insulin infusion at night with a relatively uniform and higher rate in the first half of the night from 00:00 to 03:00, and in the early morning hours

Table 1

Characteristics of study groups (mean ± SD)

Characteristic	Group 1 (0–6 yrs.)	Group 2 (6–12 yrs.)	Group 3 (12–18 yrs.)
Number of subjects	23	39	76
Age at the time of examination, years	3.8±1.5	9.6±1.5	15.4±1.6
Duration of T1D, years	1.5±0.9	3.9±2.5	5.9±3.5
HbA_{1c}, %	8.3±1.2	9.3±1.6	9.4±1.7
Height, cm	103.8±9.1	138.0±10.3	166.5±8.7
Weight, kg	16.5±4.1	32.3±7.2	57.4±10.1
TDD, IU/day	10.63±0.64	23.8±9.5	47.0±13.8
TDD/kg, IU/kg/day	0.64±0.13	0.74±0.18	0.82±0.25
Daily dose of basal insulin, IU/day	3.2±1.4	9.5±5.5	20.7±5.2
Ratio of daily basal and bolus insulin requirements, %/%	29/71	40/60	44/56

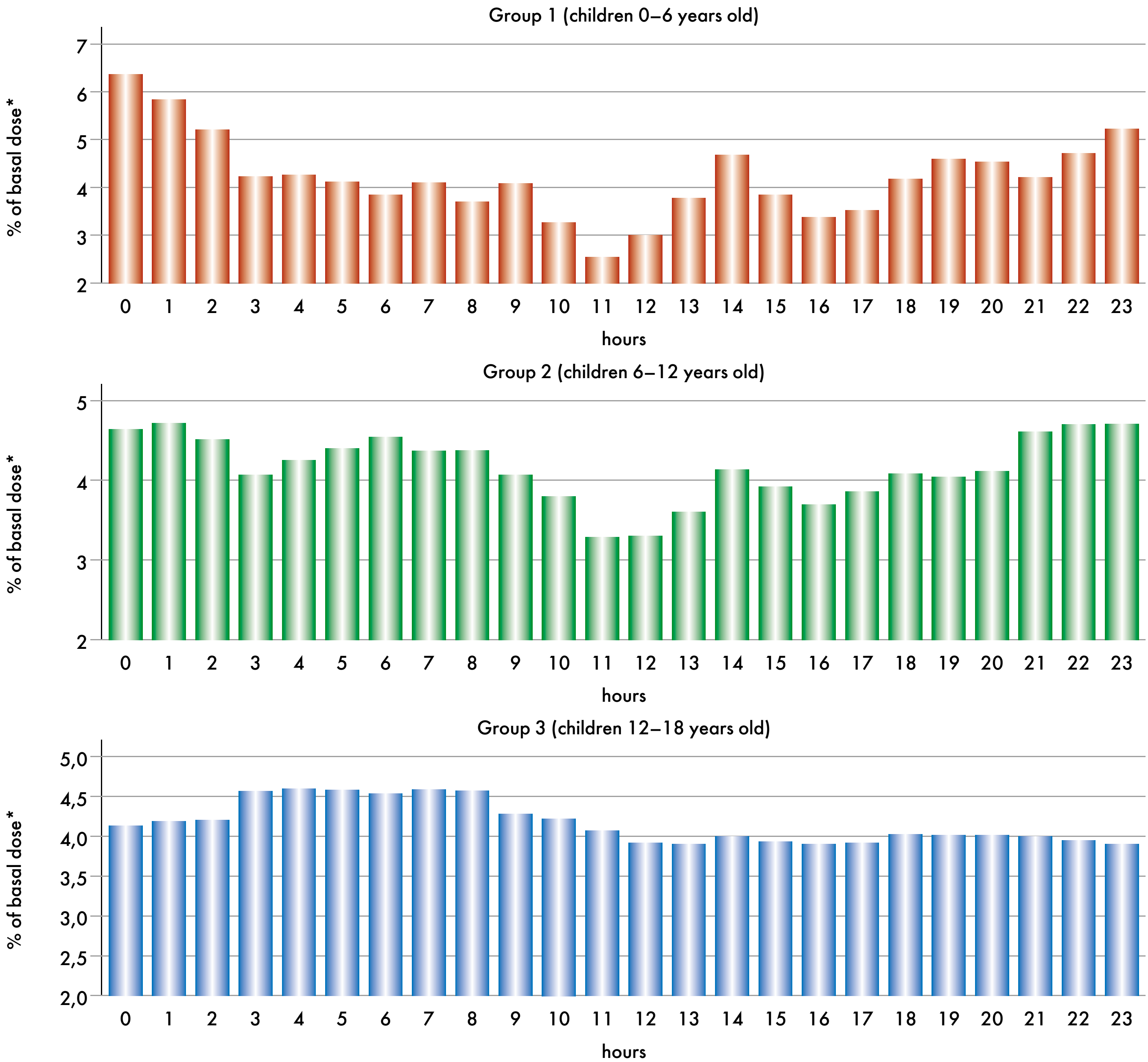

Figure 1. Profiles of basal insulin infusion in the examined groups of patients. Mean values for each group (Me) are demonstrated.
*** Basal dose is the average daily insulin dose administered with pump in basal mode.**

from 05:00 to 08: 00. In the daytime basal insulin infusion rate also decreased but this decrease was less marked than in the first age group.

- In the third age group, the maximum basal insulin infusion rate was in the second half of the night and in the early morning hours from 04:00 to 08:00, in the rest hours the infusion rate remained relatively uniform.

Thus, profile of basal insulin infusion in the second age group is intermediate between the 1st and 3rd groups with some features of both groups.

In all age groups CarbF and ISF values were found to be dependent on the time of day. Thus, the highest CarbF was registered in the morning hours in all groups, and the lowest CarbF – in the evening hours (Table 2). Regarding ISF, the inverse relationship was observed; it also reflected the greater needs in the bolus insulin (for hyperglycemia correction) in the morning. In addition, higher age was characterized by significant CarbF increase and ISF decrease. Actual ISF and ISF values matched the estimated parameters in no group, and were statistically and clinically significantly different ($p<0.05$).

Conclusions

these results suggest that TDD, ratio of basal and bolus TDD, and circadian profile of insulin requirements and insulin sensitivity is largely dependent on age. Obtained coefficients for bolus insulin doses calculation significantly differ from the values obtained using the most well-known formulas.

Table 2

Actual and estimated values of the carbohydrate factor and insulin sensitivity factor (mean ± SD)				
Parameter	Time of the day	Group 1	Group 2	Group 3
Actual CarbF	8.00–13.00	0.9±0.4*	1.2±0.5*	1,8±0,6*
	13.00–17.00	0.8±0.5*	1.0±0.3*	1,6±0,7*
	17.00–21.00	0.7±0.3*	0.9±0.3*	1,5±0,6*
Estimated CarbF ("2.6 rule")		1,14±0,34	1.28±0.32	1.43±0.43
Empirical constant for CarbF calculation		1,26±0,71	1.39±0.37	1.99±0.67
Actual ISF	6.00–13.00	12.4±9.0*	8.2±3.5*	3,8±1,6*
	13.00–17.00	12.7±7.6*	8.5±3.5*	4,0±1,6*
	17.00–21.00	13.4±7.6*	8.5±3.7*	4,0±1,8*
Estimated ISF ("2000 rule")		11,7±3,9	5.2±1.6	2.6±0.9
Empirical constant for ISF calculation		126±82	182±66	184±102.8

Note: * statistically significant difference between actual and estimated value is, $p < 0.05$

Thus, when transferring patients to intensive basal-bolus insulin therapy via CSII, formulas used to calculate factors should be modified to customize insulin pump according to age.

CarbF should be calculated as follows:

- children 0 to 6 years old — CarbF [IU/CU] = (1.25 × TDD) / weight(kg);
- children 6 to 12 years old — CarbF [IU/CU] = (1.4 × TDD) / weight(kg);
- children 12 to 18 years old — CarbF [IU/CU] = (2.0 × TDD) / weight(kg).

ISF should be calculated as follows:

- children 0 to 6 years old — ISF [mmol/l/IU] = 125 / TDD;
- children 6 to 12 years old — ISF [mmol/l/IU] = 180 / TDD;
- children 12 to 18 years old — ISF [mmol/l/IU] = 180 / TDD.

Proportion of basal insulin should be:

- children 0 to 6 years old — 30–35% TDD;
- children 6 to 12 years old — 35–40% TDD;
- children 12 to 18 years old — 45–50% TDD.

Programming the individual 'floating' profile of the basal insulin delivery age-related features should be taken into account:

- children 0 to 6 years old need higher infusion rate at 22:00–03:00, and lower infusion rate at 11:00–13:00;
- children 6 to 12 years old need higher infusion rate at 22:00–3:00 and 04:00–9:00;
- children 12 to 18 years old may need higher infusion rate at 04:00–09:00.

Discussion

current recommendations for insulin pump customization (profile of basal insulin delivery, and coefficients for BC programming) are mostly based on studies of adult T1D patients and do not always take into account individual differences and age. Thus, many studies described and proposed physiological justification [25] of age-dependent features not only for daily insulin requirements, but for basal / bolus insulin ratio required to maintain optimal glycemic control. The underlying mechanisms of these differences may be responsible also for typical differences of coefficients to calculate a bolus insulin dose throughout the day.

According to various international and national recommendations, 30 to 50% of the TDD is recommended for basal delivery when transferring patients to intensive basal-bolus insulin therapy via CSII [1, 19]. According to our data, the daily dose of basal insulin should be 29–44% of the TDD, depending on age (this figure should increase with age) to maintain target blood glucose. These results are generally consistent with international studies.

Profile of basal insulin delivery also has age-appropriate features. Young children need higher rate of insulin infusion in the evening and in the first half of the night, while in the daytime infusion rate should be relatively minimal. As the age increases, the need in higher rate of basal insulin infusion appears in the early morning hours, due to dawn phenomenon. International studies describe a biphasic profile of basal insulin delivery for all age groups, with more needs in relatively high rate of insulin infusion in the evening (sunset phenomenon) in young children and in the morning (dawn phenomenon) – in adolescents and young T1D patients. In our study significant biphasic profile of insulin delivery was found only in children 6–12 years old, young children needed higher rate of basal insulin infusion in the evening (sunset phenomenon), and adolescents – in the second half of the night and in the morning (dawn phenomenon).

According to the obtained data, the previously proposed formulas for customizing BC settings do not allow to calculate the correct values, depending on TDD, and body weight for children according to their age. Consequently, the optimal individual BC settings according to patient's age may be calculated with implementation of additional factors to the formula in the form of empirical constants.

This study is exploratory in nature, the empirical coefficients and constants are preliminary and require further clarification. Obtaining reliable correction factors to account for age differences in when customizing insulin pumps settings is possible only after prospective studies with a larger number of subjects and endpoints assessment in terms of glycemic control (HbA_{1c}). In present study no mathematical comparison of the basal insulin delivery profiles with those recommended by

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Renner R. was conducted due the limited sample size in each of the age groups. However, such a comparison is useful in the future, since the results may be interesting to practicing endocrinologists. Despite the limitations of the study, obtained data may be used for customizing initial insulin pump settings with subsequent correction according to results of glycemic control.

The authors declare no conflict of interest related to the data in this manuscript.

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