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Glycaemic control and prevalence of hypoglycaemic events in children and adolescents with type 1 diabetes mellitus treated with insulin analogues

Glikemijska kontrola i prevalencija hipoglikemija kod dece i adolescenata sa dijabetesom melitusom tipa 1 lečenih insulinskim analozima

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Abstract

Background/Aim. An ideal insulin regimen for children and adolescents with type 1 diabetes mellitus (T1DM) should be physiological, flexibile and predictable, protecting against hypoglycaemia. The aim of this study was to evaluate the influence of insulin analogues on glycaemic control and the occurance of hypoglycaemic episodes in children and adolescents with T1DM. **Methods.** The study group consisted of 151 children and adolescents (90 boys, 61 girls) treated with human insulins for at least 12 months before introducing insulin analogues. All the patients were divided into two groups: the group I consisted of 72 (47.7%) patients treated with three injections of regular human insulin before meals and long-acting analogue (RHI/LA), and the group II of 79 (52.3%) patients treated with a combination of rapid-acting and long-acting analogue (RA/LA). The levels of glycated hemoglobin (HbA1c) and the number of hypoglycaemic episodes were assessed at the beginning of therapy with insulin analogues, and after 6 and 12 months. **Results.** The mean HbA1c was significantly lower in the group I (RHI/LA) after 6 months (9.15% *vs* 8.20%, $p < 0.001$) and after 12 months (9.15% *vs* 8.13%, $p < 0.001$) as well as in the group II (RA/LA) after 6 months (9.40% *vs* 8.24%, $p < 0.001$) and after 12 months of insulin analogues treatment (9.40% *vs* 8.38%, $p < 0.001$). The frequency of severe hypoglycaemia was significantly lower in both groups after 6 months (in the group I from 61.1% to 4.2% and in the group II from 54.4% to 1.3%, $p < 0.001$), and after 12 months (in the group I from 61.1% to 1.4% and in the group II from 54.4% to 1.3%, $p < 0.001$). **Conclusion.** Significantly better HbA1c values and lower risk of severe hypoglycaemia were established in children and adolescents with T1DM treated with insulin analogues.

Key words:
diabetes melitus, type 1; child; adolescent; hypoglycemia; insulin; treatment outcome.

Apstrakt

Uvod/Cilj. Idealan insulinski režim za decu i adolescente sa dijabetesom melitusom tipa 1 (DMT1) trebalo bi da bude fiziološki, fleksibilan i predvidljiv, kao i da štiti od hipoglikemija. Cilj ove studije bio je procena uticaja insulinskih analoga na stepen glikemijske kontrole i učestalost hipoglikemijskih epizoda kod dece i adolescenata sa DMT1. **Metode.** Ciljna grupa obuhvatila je 151 dete i adolescenta (90 dečaka, 61 devojčica) koji su dobijali humane insuline bar 12 meseci pre uvođenja insulinskih analoga. Bolesnici su bili podeljeni u dve grupe: u prvoj je bilo 72 (47,7%) dece lečene sa tri injekcije regularnog humanog insulina pre obroka i dugodelujućim analogom insulina (RHI/DA), a u drugoj grupi 79 (52,3%) dece lečene kombinacijom brzodelujućeg i dugodelujućeg analoga insulina (BA/DA). Nivoi HbA1c i broj hipoglikemijskih epizoda registrovani su na početku terapije insulinskim analozima, i posle 6 i 12 meseci. **Rezultati.** Srednja vrednost glikoziranog hemoglobina (HbA1c) bila je značajno niža u prvoj grupi (RHI/DA) posle 6 meseci (9,15% *vs* 8,20%, $p < 0,001$) i posle 12 meseci (9,15% *vs* 8,13%, $p < 0,001$), kao i u drugoj grupi (BA/DA) posle 6 meseci (9,40% *vs* 8,24%, $p < 0,001$) i posle 12 meseci lečenja insulinskim analozima (9,40% *vs* 8,38%, $p < 0,001$). Učestalost teških hipoglikemija bila je značajno niža u obe grupe posle 6 meseci (u prvoj grupi sa 61,1% na 4,2% i u drugoj sa 54,4% na 1,3%, $p < 0,001$) i posle 12 meseci (u prvoj grupi sa 61,1% na 1,4% i u drugoj sa 54,4% na 1,3%, $p < 0,001$). **Zaključak.** Kod dece i adolescenata sa DMT1 lečenih insulinskim analozima utvrđen je značajno niži nivo HbA1c i manji rizik od teških hipoglikemija.

Ključne reči:
dijabetes melitus, tip 1; deca; adolescenti; hipoglikemija; insulin; lečenje, ishod.

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Introduction

Ideally, insulin regimen for children and adolescents with type 1 diabetes mellitus (T1DM) should be physiological, flexibile, and predictable, in order to protect against hypoglycaemia [1, 2]. This goal is particularly difficult to achieve in the paediatric patients, due to their susceptibility to hypoglycaemia, fluctuating insulin requirements caused by exercise, illness, variable carbohydrate intake, psychosocial and physiologic issues related to age, puberty, and weight gain [3, 4]. The Diabetes Control and Complications Trial (DCCT) and other landmark studies have shown that intensive insulin therapy is associated with an increased risk of hypoglycaemia [3].

Compared to regular human insulin (RHI), the new rapid-acting insulin analogues (RA, insulin aspart and lispro) more closely resemble postprandial endogenous insulin secretion by their faster onset and shorter duration of action which reduces the risk of hypoglycaemia between meals and during the first part of night as well as a need for snacks between meals [5, 6].

Long-acting insulin analogues (LA, insulin detemir and glargine), have been developed with the aim of providing a constant, flat and reproducible supply of basal insulin. Their action starts within 1 to 2 hours and diminishes within 16 to 24 hours, with no pronounced peaks, which lowers the risk of diurnal and nocturnal hypoglycaemia [4, 7, 8].

The aim of this retrospective study was to evaluate the influence of rapid-acting and long-acting insulin analogues on metabolic control and frequency of hypoglycaemic events in children and adolescents with T1DM.

Methods

The study group consisted of 151 children and adolescents (90 boys, 61 girls) treated with human insulins (total daily dose ≤ 1.5 U/kg) (Table 1). The primary inclusion criterion was intensive treatment with human insulins for at least 12 months. The second inclusion criterion was introducing insulin analogues due to unsatisfactory metabolic control. All the patients were divided into two groups: the group I consisted of 72 (47.7%) children treated with three injections of regular human insulin before meals and long-acting analogue (insulin detemir or glargine) at bedtime (RHI/LA) and the group II of 79 (52.3%) children treated with rapid-acting analogue (insulin aspart) as premeal insulin and long-acting analogue at bedtime (RA/LA). The mean age of patients at the beginning of treatment with insulin analogues was 13.0 ± 2.2 years in the group I and 13.5 ± 2.4 years in the group II. A follow-up period for all the subjects was 12 months, excluding 8 patients who were lost for follow-up after 6 months because of transfer to adult endocrinologist.

In this observational, retrospective study data were collected from medical records. The levels of glycated hemoglobin (HbA1c) and the number of hypoglycaemic episodes were assessed at the beginning, and 6 and 12 months after introducing insulin analogues. Hypoglycaemic episodes were classified as minor (child could help itself) and major – severe (requiring assistance to treat).

All data were analysed using the statistical package SPSS (version 17.0). Data were reported as absolute numbers and percentages, or as means and standard deviations (SDs). Student's *t*-test was used to assess the statistical significance of differences between different insulin regimens and between the groups. Pearson's χ^2-test was used for comparison of categorical variables. Changes in the means of frequency and severity of hypoglycemic episodes were assessed using Friedman and Wilcoxon signed ranks tests. *p*-values of less than 0.05 were considered as statistically significant.

Results

The mean HbA1c was significantly lower in both groups after 6 and 12 months. In the group I (RHI/LA) HbA1c was lower after 6 months (9.15% *vs* 8.20%) and after 12 months (9.15% *vs* 8.13%) as well as in the group II (RA/LA) after 6 months (9.40% *vs* 8.24%) and after 12 months of insulin analogues treatment (9.40% *vs* 8.38%) as shown in Table 2. There were no significant statistical differences in HbA1c between the groups at the beginning and 6 and 12 months after introducing insulin analogues.

The frequency of hypoglycaemic episodes was significantly lower in both groups 6 months after introducing insulin analogues (100% to 87.5% in the group I, and 100% to 89.9% in the group II), and 12 months after introducing analogues (100% to 83.3% in the group I, and 100% to 75.9% in the group II). The frequency of minor hypoglycaemic events was higher in both groups (Table 3) after 6 months (in the group I from 38.9% to 83.3%, and in the group II from 45.6% to 88.6%) and after 12 months (in the group I from 38.9% to 76.4%, and in the group II from 45.6% to 69.9%) while the frequency of severe hypoglycaemic events was significantly lower in both groups after 6

Table 1

Baseline characteristics of the 151 children and adolescents with type 1 diabetes mellitus

Patients characteristics	Regular human insulin/Long-acting analogue (RHI/LA)	Rapid-acting analogue/Long-acting analogue (RA/LA)
All children, n (%)	72 (47.7)	79 (52.3)
Boys, n (%)	47 (65.3)	43 (54.4)
Girls, n (%)	25 (34.7)	36 (45.6)
Age of introducing analogues (years), $\bar{x} \pm SD$	13.0 ± 2.2	13.5 ± 2.4
HbA1c (%), $\bar{x} \pm SD$	9.15 ± 2.24	9.40 ± 1.67

Table 2

Glycated hemoglobin (HbA1c) before introducing insulin analogues and after 6 and 12 months

Insulin therapy	HbA1c (%), $\bar{x} \pm SD$			Difference	95% CI	*p*-value
	before	after 6 months	after 12 months			
RHI/LA	9.15 ± 2.25	8.20 ± 1.71		0.96	(0.6–1.2)	< 0.001
			8.13 ± 1.63	1.01	(0.6–1.3)	< 0.001
RA/LA	9.40 ± 1.67	8.24 ± 1.47		1.16	(0.9–1.4)	< 0.001
			8.38 ± 1.66	1.04	(0.7–1.4)	< 0.001

RHI/LA – Combination of regular human insulin (RHI) and long-acting analogue (LA); RA/LA – Combination of rapid-acting analogue (RA) and long-acting analogue (LA).

Table 3

The frequency of hypoglycaemic events 6 and 12 months after introducing insulin analogues

Insulin therapy		Hypoglycaemic events, n (%)			
		without	minor	severe	*p* value
RHI/LA	Before	0	28 (38.9)	44 (61.1)	
	After 6 months	9 (12.5)	60 (83.3)	3 (4.2)	< 0.0001
	After 12 months	12 (16.7)	55 (76.4)	1 (1.4)	< 0.0001
RA/LA	Before	0	36 (45.6)	43(54.4)	
	After 6 months	8 (10.1)	70 (88.6)	1 (1.3)	< 0.0001
	After 12 months	19 (24.1)	55 (69.9)	1 (1.3)	< 0.0001
Total	Before	0	64 (42.4)	87 (57.6)	
	After 6 months	17 (11.3)	130 (86.1)	4 (2.6)	< 0.0001
	After 12 months	31 (20.5)	110 (72.8)	2 (1.3)	< 0.0001

RHI/LA – Combination of regular human insulin (RHI) and long-acting analogue (LA); RA/LA – Combination of rapid-acting analogue (RA) and long-acting analogue (LA).

months (in the first group decreased from 61.1% to 4.2%, and in the group II from 54.4% to 1.3%) and after 12 months (in the group I from 61.1% to 1.4%, and in the group II from 54.4% to 1.3%). There were no statistically significant differences in frequency of hypoglycaemic episodes between the groups at the beginning, and 6 and 12 months after introducing insulin analogues.

Discussion

It is widely accepted that the traditional insulins used in basal-bolus therapy, regular human and neutral protamine hagedorn (NPH) insulin, do not accurately reproduce the physiological insulin profile. Insulin analogues have demonstrated certain clinical improvements over regular human insulin, and NPH insulin [9–11]. Data indicate that the combination of rapid-acting and long-acting analogues leads to overall improved glycaemic control in T1DM [5, 11, 12].

The risk of hypoglycaemia is the most feared adverse event among diabetes mellitus patients and medical staff in relation to insulin treatment [13, 14]. Severe hypoglycaemia may lead to long-term cognitive impairment in children below 6 years of age and similar effects may also apply for older children [15, 16]. Treatment with insulin analogues is associated with lower risk of hypoglycaemia, especially severe ones, in children and adolescents with T1DM. It is likely that a combination of rapid-acting and long-acting insulin analogues produces a more physiological insulin secretion and thereby reduces the risk of severe hypoglycaemia [12].

In this retrospective study all the patients were already on basal-bolus therapy recieving three injections of regular human insulin before meals and NPH insulin at bedtime. Introducing long-acting insulin at bedtime or the combination of mealtime rapid-acting and bedtime long-acting insulin analogue resulted in improved glycaemic control with lower risk of severe hypoglycaemia. The patients in both groups experienced a decrease in HbA1c levels after introducing insulin analogues with a small, but statistically significant difference of 0.96% in the group I and 1.16% in the group II after 6 months, and 1.01% and 1.04% after 12 months. The mean HbA1c levels were still significantly lower 12 months after introducing insulin analogues in both groups. The frequency of severe hypoglycaemia was significantly lower in both groups 6 and 12 months after introducing insulin analogues, but there were no statistically significant differences between the groups. There were more patients with minor hypoglycaemia, but those were ones that had severe hypoglycaemic events before introducing insulin analogues.

In the large-scale multicentre trial, Hermansen et al. [5] showed that combination of insulin analogues, insulin detemir and insulin aspart, in addition to a significant improvement in HbA1c, provides a lower risk of hypoglycaemia than NPH and regular human insulin treatment. A meta-analytsis of the Cochrane Metabolic and Endocrine Disorders Group reviewed 42 randomized controlled trials that compared the effect of intensified therapy regimens with rapid-acting insulins to regular insulin in adults. The analyses demonstrated a small, but statistically significant decrease in HbA1c using rapid-acting insulin analogues [6, 17]. They mimic the normal mealtime insulin response more closely than injection of regular human insulin and thereby improve postprandial glycaemic control [5, 10].

There are limited data regarding the use of rapid-acting and long-acting insulin analogues in children and adolescents

compared to adults with T1DM. None showed a significant decrease in HbA1c levels, and only one demonstrated lower rates of hypoglycaemic episodes. Only few studies showed a significant decrease in morning fasting blood glucose levels and in the frequency of severe diurnal and nocturnal hypoglycaemic episodes [18]. Chase et al. [19] demonstrated a decrease of HbA1c in addition to a significant decrease in severe hypoglycaemia. In the first large-scale multicentre study Robertson et al. [2] showed the efficancy and safety of insulin detemir in children and adolescents with T1DM. The lower risk of severe hypoglycaemia with insulin detemir was achieved in children without compromising glycaemic control. In all age groups the quality of life seemed to improve with the insulin analogues, which was attributed to less fear of hypoglycemia and more flexibility in lifestyle and food intake [4, 6, 17, 19].

Conclusion

This study demonstrated that insulin analogues used in basal-bolus therapy, either only long-acting analogues with premeal regular human insulin or the combination of rapid-acting and long-acting analogues, provide significantly better HbA1c values and lower risk of severe hypoglycaemic events in children and adolescents with T1DM.

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