Continuous glucose monitoring is a helpful tool for the modification and assessment of such a modified treatment of type 1 diabetes mellitus in children and adolescents

Przydatność ciągłego monitorowania glikemii do modyfikacji oraz oceny tak zmienionego leczenia cukrzycy typu 1 u dzieci i młodzieży

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Wstęp. *Monitorowanie glikemii stanowi zasadniczy element intensywnej insulinoterapii w cukrzycy typu 1 (T1DM).* ***Cele.*** *Celem niniejszej prospektywnej pracy klinicznej było 1) modyfikacja leczenia cukrzycy w grupie dzieci i młodzieży z T1DM na podstawie wyników ciągłego monitorowania glikemii (CGM); 2) zastosowanie CGM do oceny tak zmienionego leczenia.* ***Pacjenci i metody.*** *U 61 chorych z T1DM (30 dziewcząt), w średnim wieku 12 lat i 4 miesiące, dwukrotnie – na początku badania oraz po okresie 3 miesięcy – wykonano ciągłe monitorowanie glikemii oraz oznaczono odsetek hemoglobiny glikowanej (HbA1c). Na podstawie wyników pierwszego CGM, u każdego pacjenta wprowadzono zmiany w insulinoterapii.* ***Wyniki.*** *Odsetek chorych, u których stwierdzono występowanie epizodów hipoglikemii oraz hiperglikemii, nie uległ istotnej zmianie w trakcie trwania badania, i wynosił odpowiednio 93 vs 91% i 100 vs 100%. Po okresie 3 miesięcy zmodyfikowanego leczenia nie zanotowano także istotnych zmian w liczbie epizodów hipoglikemii (1,4±1,0 vs 1,3±0,9 epizodów/pacjenta/dobę, p>0,05) oraz dobowej dawce insuliny (0,89±0,25 vs 0,87±0,24 U/kg/dobę, p>0,05). Uzyskano natomiast istotne statystycznie obniżenie średniej wartości HbA1c (7,7 vs 7,3%, p<0,01) oraz liczby (2,9±1,0 vs 2,3±0,8 epizodów/pacjenta/dobę, p<0,001) i czasu trwania epizodów hiperglikemii (7,3±3,4 vs 5,7±3,1 godzin/pacjenta/dobę, p<0,01).* ***Wnioski.*** *Ciągłe monitorowanie glikemii jest pomocne w obniżeniu odsetka HbA1c, któremu nie towarzyszy wzrost dobowej dawki insuliny czy też zwiększone ryzyko wystąpienia hiperglikemii lub hipoglikemii. Należy jednak zaznaczyć, że większość dzieci i młodzieży z cukrzycą typu 1 doświadcza patologicznych dobowych wahań glikemii, pomimo poprawy kontroli cukrzycy, mierzonej spadkiem odsetka HbA1c.*

Słowa kluczowe: *ciągłe monitorowanie glikemii, hipoglikemia, hiperglikemia, cukrzyca typu 1, HbA1c*

Background. *Glucose monitoring constitutes an essential part of intensive management of type 1 diabetes mellitus (T1DM).* ***Objectives.*** *This prospective, clinical study was aimed to: 1) modify the treatment of T1DM in a group of children and adolescents, based on the results provided by the continuous glucose monitoring (CGM); 2) use CGM for the assessment of such a modified treatment.* ***Subjects and methods.*** *61 patients with T1DM (30 girls), at the mean age of 12.4 years were studied. CGM and glycohemoglobin (HbA1c) measurement were performed twice: at the study entry and after a 3-month period. Based on the results of the first CGM insulin therapy was modified in all the participants.* ***Results.*** *The percentage of patients experiencing hypoglycemias and hyperglycemias did not change significantly throughout the study, 93 vs 91%, and 100 vs 100%, respectively. After a 3-month period of modified treatment, there was no change in either the number of hypoglycemic episodes (1.4±1.0 vs 1.3±0.9 episodes/patient/day, p>0.05) or daily insulin dose (0.89±0.25 vs 0.87±0.24 U/kg/day, p>0.05). Yet, there was a significant decrease in mean HbA1c (7.7 vs 7.3%, p<0.01) and in the number (2.9±1.0 vs 2.3±0.8 episodes/patient/day, p<0.001) and duration of hyperglycemic episodes (7.3±3.4 vs 5.7±3.1 hours/patient/day, p<0.01).* ***Conclusions.*** *CGM is helpful in improving HbA1c, without increasing insulin dose or the risk of hyperglycemic or hypoglycemic episodes. However, majority of children and adolescents with T1DM develop pathological glucose excursions in spite of the improvement in glycemic control (shown as a decline in HbA1c).*

Key words: *continuous glucose monitoring, hypoglycemia, hyperglycemia, type 1 diabetes mellitus, HbA1c*

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List of the abbreviations

type 1 diabetes mellitus (T1DM), continuous glucose monitoring (CGM), glycohemoglobin A1c (HbA1c), body mass index (BMI), multiple daily injections (MDI), continuous subcutaneous insulin infusion (CSII), neutral protamine Hagedorn (NPH), self-monitoring of blood glucose (SMBG).

Introduction

In the last decades, a constant increase in the annual incidence of childhood type 1 diabetes mellitus (T1DM) has been observed worldwide [1], especially in the youngest age group (below 5 years of life). In Finland, where the incidence rate is the highest, in last years it exceeded 40 per 100 000, in the age group up to 14 years. Our own epidemiological data from the Krakow region, South Poland, for the year 2003 indicate the incidence rate of 13.7 per 100 000, which is approximately 3 times higher than it used to be in 1989 (4.7/100 000) [2]. In 2006, the United Nations together with IDF (*International Diabetes Federation*) passed a resolution recognizing diabetes mellitus as a global epidemic, which demands an international search for global solution. It was proven that late microvascular complications can be prevented or delayed by good glycemic control and intensive insulin therapy in adolescents and adults with T1DM [3, 4]. Other studies demonstrated the same effect for children before and during puberty [5, 6]. A tight control, however, was associated with an increased risk of severe hypoglycemia [7]. Therefore, there is a great need for improving glycemic control and safety of treatment in children and adolescents with T1DM. Rapid acting and long acting insulin analogs, as well as pomp therapy seem to facilitate the achievement of these goals [8, 9]. Nevertheless, progress should be made not only in the development of new insulin preparations or methods of insulin administration, but also in self-monitoring of blood glucose, which constitutes an essential part of intensive insulin therapy. Continuous glucose monitoring (CGM), which provides a new insight into daily glucose profiles for a diabetic team and a patient, might be an option.

The purpose of this study was 1) to use the results provided by CGM for modification of the treatment in a group of children and adolescents with T1DM, and 2) to assess the implementation of that alteration by means of CGM.

Materials and methods

Children and adolescents with T1DM diagnosed according to the WHO criteria [10] and followed-up in the Department of Pediatric and Adolescent Endocrinology, Krakow, Poland, were invited to participate in this prospective clinical study if they were at the age between 2 and 18 years, were treated with insulin for at least 9 months and had no other chronic diseases, except from primary hypothyroidism in euthyroid state. Sixty-one consecutive patients, who had first given their written, informed and witnessed consent, were included into the study. All clinical procedures were completed between February 2004 and September 2005. The characteristics of the studied group are given in table 1.

Glycohemoglobin and continuous glucose monitoring

Glycohemoglobin (HbA1c) was measured in capillary blood, in one laboratory, using the reference method of high performance liquid chromatography which had been certified by the NGSP (National Glycohemoglobin Standardization Program). The normal range fell within 4.2–6.3%. Continuous glucose monitoring was performed using the system produced by MINIMED, USA, which was described in details elsewhere [11]. In general, the CGM system measured continuously, for 3–4 subsequent days, glucose concentration in the interstitial fluid of the subcutaneous fat tissue. Records of the mean glucose values, within the range of 40–400 mg/dl, were made every 5 minutes, which gave 288 glycemic results per 24 hours. When the monitoring was finished, the stored data were retrospectively analyzed by a special software. Hypoglycemia was defined as blood glucose $\leq$ 60 mg/dl (3.3 mmol/l) and hyperglycemia as values $\geq$ 180 mg/dl (10 mmol/l). For both hyperglycemias and hypoglycemias, the number of episodes per patient per day, as well as the duration in hours per patient per day was calculated.

Research design

At the study entry, all the 61 patients underwent the first continuous glucose monitoring (CGM-1) in an ambulatory setting. HbA1c was also measured in all the subjects. The results of CGM-1 were analyzed by the same physician and discussed with the patients and their families. If appropriate, changes in diabetes therapy were introduced. After a 3-month period of such modified treatment, HbA1c was checked again in all the subjects and the second ambulatory CGM (CGM-2) was performed in 56 patients (92% of the studied group, 29 girls and 27 boys). Five patients, who did not undergo the second CGM because of family problems, did not differ in age, diabetes duration or HbA1c value from those patients who completed the repeated CGM.