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Short-term use of continuous glucose monitoring system adds to glycemic control in young type 1 diabetes mellitus patients in the long run: A clinical trial

Kratkotrajna primjena kontinuiranog mjerenja glikemije poboljšava metaboličku kontrolu kod djece i adolescenata sa dijabetesom melitusom tip 1 na duži period: kliničko ispitivanje

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Abstract

Background/Aim. Balancing strict glycemic control with setting realistic goals for each individual child and family can optimize growth, ensure normal pubertal development and emotional maturation, and control long term complications in children with type 1 diabetes (T1DM). The aim of this study was to evaluate the efficacy of short-term continuous glucose monitoring system (CGMS) application in improvement of glycemic control in pediatric type 1 diabetes mellitus (T1DM) patients. **Methods.** A total of 80 pediatric T1DM patients were randomly assigned into the experimental and the control group. The experimental group wore CGMS sensor for 72 hours at the beginning of the study. Self-monitored blood glucose (SMBG) levels and hemoglobin A1c (HbA1c) levels were obtained for both groups at baseline, and at 3 and 6 months. **Results.** There was a significant improvement in HbA1c ($p < 0.001$), in both the experimental and the control group, without a significant difference between the groups. Nevertheless, after 6 months the improvement of mean glycemia was noticed only in the experimental group. This finding was accompanied with a decrease in the number of hyperglycemic events and no increase in the number of hypoglycemic events in the experimental group. **Conclusions.** The results suggest that the CGMS can be considered as a valuable tool in treating pediatric T1DM patients, however further research is needed to more accurately estimate to what extent, if any, it outperforms intensive self-monitoring of blood glucose.

Key words:
diabetes mellitus, type 1; adolescent; child; child, preschool; blood glucose self-monitoring.

Apstrakt

Uvod/Cilj. Balansiranjem stroge glikemijske kontrole sa postavljanjem realnih ciljeva za svako pojedinačno dete i porodicu može se optimizirati rast, odrediti normalan razvoj u pubertetu, kao i emocionalno sazrevanje i dugoročna kontrola komplikacija kod dece sa dijabetesom tip 1 (T1DM). Cilj ove studije bio je da se procijeni efikasnost metoda kontinuiranog supkutanog mjerenja glukoze u postizanju bolje glikemijske kontrole kod djece i adolescenata sa dijabetesom melitusom tip 1. **Metode.** Ukupno 80 djece sa dijabetesom melitusom tip 1 slučajnim odabirom određeno je u eksperimentalnu ili kontrolnu grupu. Ispitanici u eksperimentalnoj grupi nosili su aparat za kontinuirano praćenje glikemije (CGMS aparat) 72 sata na početku studije. Za ispitanike iz obje grupe evidentirani su podaci samokontrolisane glikemije (SMBG) i hemoglobina A1c (HbA1c) na početku studije, nakon tri i nakon šest mjeseci. **Rezultati.** Dobijeno je značajno poboljšanje koncentracije HbA1c na tri i šest mjeseci i u eksperimentalnoj i kontrolnoj grupi ($p < 0{,}001$), bez značajne razlike među grupama. Nasuprot tome, značajno sniženje srednje glikemije nakon šest mjeseci zabilježeno je samo u eksperimentalnoj grupi. Nadalje, u eksperimentalnoj grupi došlo je i do smanjenje broja hiperglikemijskih događaja, a, pri tom, nije evidentiran porast broja hipoglikemijskih događaja. **Zaključak.** Rezultati studije sugerišu da sistem kontinuiranog supkutanog praćenja glikemije može biti korisno sredstvo metaboličke kontrole kod djece sa dijabetesom melitusom tip 1, ali neophodna su dodatna istraživanja kako bi se preciznije utvrdilo u kojoj mjeri, ako je to uopšte slučaj, ovaj metod, u terapeutskom smislu, nadmašuje intenzivno samokontrolisanje glikemije.

Ključne reči:
dijabetes melitus, insulin-zavisni; adolescent; deca; deca predškolska; glukoza u krvi, samopraćenje.

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Introduction

Balancing strict glycemic control with setting realistic goals for each individual child and family can optimize growth, ensure normal pubertal development and emotional maturation, and control long term complications in children with type 1 diabetes (T1DM) [1, 2]. The goal of the usual intensive therapy is to maintain near-normal glycemia, normalize hemoglobin A1c (HbA1c), control postprandial glycemic excursion and decrease the number of hypoglycemic events. Although very useful, multiple, four daily blood glucose measurements are still insufficient to provide and predict all relevant glycemic fluctuations. A newer method of continuous glucose monitoring (CGMS) seems to address the issue [3]. The CGMS provides the maximal amount of data about glycemic profile during activities of daily living, including physical activity, work, meals, and sleep. Thus, continuous monitoring have a great potential value to improve glycemic control while decreasing the incidence of hypoglycemia, especially in a patient with poorly controlled diabetes and those who are at the high risk of severe hypoglycemia. The benefits of CGMS use in T1DM patients have been shown in multiple studies [4–11].

Our study was conducted to analyze whether a three-day use of CGMS can significantly contribute to therapeutic decisions and thus to glycemic control over and above information provided by the standardized blood glucose self-monitoring in young T1DM patients.

Methods

The participants for this single-blinded randomized clinical trial were recruited from T1DM patients in the Children's Hospital in Banja Luka, Bosnia and Herzegovina. The study which lasted for 6 months was completed in 2007. It was approved by the Ethics Committee of Human Experimentation of Bosnia and Herzegovina. A total of 80 T1DM patients were randomly allocated into the experimental (CGMS and self-monitored blood glucose – SMBG) and the control (only SMBG) group. Inclusion criteria were: 1) HbA1c level ≥ 8%, 2) clinical diagnosis of insulin-dependent type 1 diabetes mellitus for at least 1 year, 3) patient's age 5 to 18 years, 4) availability for all office visits and compliance with the study protocol, and 5) compliance to wear a medical device for 72 consecutive hours. All the patients were using insulin aspart as their ultra short-acting insulin and insulin detemir as long-acting insulin in their therapy. Most of the patients (70%) in both groups were on intensive insulin therapy (using multiple injections per day – MDI), while the rest of them (30%) followed convential therapy (using three insulin injections per day – TDI). Exclusion criteria included history of comorbidities, and noncompliance with the study protocol. The parents and/or patients had given a written informed consent for the inclusion in the study. All the patients were followed up in the clinic at baseline, 3 and 6 months by the same investigator.

Both demographic and clinical data were collected using a standardized data collection form. The experimental group of the patients and families were instructed by the same investigator in the use of the CGMS device and they were asked to enter at least four daily blood glucose measures obtained with a personal glucometer into the instrument for the calibration purpose. They also entered all data regarding insulin administration, meals taken, exercise and other relevant events (e.g. hypoglycemic symptoms). The CGMS (Medtronic MiniMed, Northridge, CA) was applied for 72 hours including three overnight profiles and was well tolerated by patients in the experimental group. There was no evidence of infection or inflammation at the insertion site of the sensor. The CMGS data were analyzed using the Medtronic-MiniMed Solution Software version 3.0B (Medtronic). In both groups, the patients underwent 3 days of nine-point self-monitoring of blood glucose using an Accu-check glucometer (Roche), before and after each main meal, at bedtime, and during the night at 2 a.m. and 5 a.m. The postmeal measurements were taken within 2 hours after the preprandial measurements. Four of the SMBG tests were entered into the CGMS monitor for calibration. Sensor insertion and CGMS training as well as SMBG training were done in hospital, after which the patients returned home to their usual insulin therapy, diet and activity. Hemoglobin A1C (HbA1c) level was measured using the DCA 2000 (Bayer, Tarrytown, NY; non-diabetic range 4.3%–6.3%) at the beginning of the study and after 3 and 6 months. In the experimental group, CGMS data were collected and reviewed and therapeutic decisions during the first three months were made based on both CGMS and SMBG data, while in the control group, therapeutic decisions were made based solely on SMBG data. Different therapy recommendations were given based on the obtained data: e. g. change in dosage of rapid-acting insulin, change in dosage of long-acting insulin, carbohydrate intake changes, or increase in physical activity. Main outcome measures considered were HbA1c, average SMBG values and numbers of hypo- and hyperglycemic events. Hypoglycemia was defined as capillary blood glucose (CBG) level lower than 3.5 mmol/L, whereas hyperglycemia was defined as CBG level higher than 10.0 mmol/L.

Raw data were summarized and expressed as counts (categorical data) or means ± standard deviations (numeric data). Bivariate relationships were estimated with Pearson's linear correlation coefficients. Group differences were assessed with the Fisher exact tests, Wilcoxon-Mann-Whitney tests (exact probabilities), Wilcoxon signed-ranks tests (exact probabilities), and Student's *t*-tests (for independent and paired samples) corrected for unequal variances, where needed. The level of statistical significance was set at $p < 0.05$ (all tests two-tailed). The Statistical Package for Social Sciences (SPSS, Chicago) was used for all statistical analyses.

Results

As can be seen from Tables 1 and 2, the experimental and control groups were similar with regard to their average body mass indexes, sex distribution, and baseline measures of HbA1c. Yet, the experimental group included on average

older children with longer diabetes duration. Furthermore, both the baseline average insulin dose, as well as the initial average glucose levels, were significantly higher in the experimental group (Tables 1 and 2). Interestingly, in neither group did the average insulin dose change noticeably during the course of the study (Table 1), despite the modifications of therapy in individual cases (Table 3 presents the most relevant modifications).

Median duration of sensor wear was 72 h in the experimental group with the average number of CGMS readings per subject equaling 864. The mean plasma glucose level measured by SMBG (10.6 ± 1.9 mmol/L) did not differ significantly from that measured by CGMS (10.6 ± 2.3 mmol/L) ($p = 0.765$). These two measures correlated highly and statistically significantly ($r = 0.86$, $p < 0.001$). In contrast, linear correlation between HbA1c and mean glycemia

Table 1

Demographic and clinical characteristics of patients (n = 80)

Characteristics	Baseline	*p**	3 months	*p**	6 months	*p**
Number of patients						
experimental group	40					
control group	40					
Female (n, %)						
experimental group	22 (55.0)	0.655				
control group	19 (47.5)					
Age (M ± SD) (yrs)						
experimental group	13.7 ± 3.3	0.016				
control group	11.8 ± 3.8					
Diabetes duration (yrs)						
experimental group	6.3 ± 4.0	0.013				
control group	4.4 ± 2.7					
Insulin (dose/kg) (M ± SD)						
experimental group	0.85 ± 0.23	0.005	0.86 ± 0.23	0.163	0.85 ± 0.22	0.150
control group	0.72 ± 0.18		0.76 ± 0.22		0.76 ± 0.23	
BMI (kg/m^2) (M ± SD)						
experimental group	19.1 ± 2.7	0.303	19.0 ± 2.6	0.438	19.6 ± 2.6	0.228
control group	18.5 ± 2.6		18.6 ± 2.5		18.9 ± 2.9	

BMI – body mass index; M – mean; SD – standard deviation;
***Statistical tests used were Fisher exact tests (sex) and *t*-tests for independent samples (age, diabetes duration, insulin/kg, BMI) – corrected for baseline levels (differences at 3 and 6 months) and unequal variances where needed**

Table 2

Changes in average hemoglobin A1C (HbA1c) and mean glycemia over 6-month period*

Period of the study	HbA1c			Mean glycemia		
	Experimental group	Control group	$p^{\dagger}$	Experimental group	Control group	$p^{\dagger}$
baseline	10.0 ± 1.6	10.2 ± 2.0	0.657	10.6 ± 1.9	9.5 ± 2.4	0.031
3 months	9.1 ± 1.5	9.4 ± 1.6	0.604	9.4 ± 2.1	9.0 ± 1.9	0.256
6 months	8.6 ± 1.2	8.9 ± 1.3	0.705	8.8 ± 1.4	9.5 ± 2.4	0.002
p Δ(1-2)‡	0.009	0.001		0.004	0.117	
p Δ(1-3)‡	< 0.001	< 0.001		< 0.001	0.813	

***The results are presented as mean ± standard deviation; †*t*-test for independent samples (between-subjects effects) controlled for baseline differences; ‡*t*-test for paired samples (within-subjects effects) examining changes from the baseline levels.**
Δ (1-2) – difference in average levels between baseline and 3-month measurement;
Δ (1-3) – difference in average levels between baseline and 6-month measurement

Table 3

Theraupetic interventions in the course of the study (n = 80)

Interventions	Experimental group		Control group	
Long-acting insuline change	25	(62.5)	20	(50.0)
increase	22	(55.0)	17	(42.5)
decrease	3	(7.5)	3	(7.5)
Rapid/short-acting insuline change	17	(42.5)	12	(30.0)
increase	15	(37.5)	9	(22.5)
decrease	2	(5.0)	3	(7.5)
Carbohydrate intake changes	15	(37.5)	9	(22.5)
Increase of physical activity	8	(20.0)	9	(22.5)

***The results are presented as frequencies and percentages (given in parentheses)**

measured by SMBG was small in magnitude, but significant ($r = 0.14$, $p = 0.032$).

At the baseline, the mean hemoglobin A1c value in the experimental group was 10.0 ± 1.6%, whereas it was insignificantly higher in the control group 10.2 ± 2.0%. A significant improvement in HbA1c was observed in both groups after 3 and 6 months ($p < 0.001$) (Table 2). However, the degree of improvement in HbA1c was not statistically significantly different between the two groups, neither at 3 months ($p = 0.604$), nor after 6 months ($p = 0.705$).

Mean glycemia (self-monitored, both groups) were significantly improved in the experimental group after 3 and 6 months (both $p = 0.01$) (Table 2). In the control group, there was an initial decrease in mean glycemia after 3 months, which was not significant ($p = 0.117$), but after 6 months mean glycemia reversed back almost to the baseline level ($p = 0.813$, compared to the baseline). No significant difference in mean glycemia between two groups was found after 3 months ($p = 0.256$); nonetheless, mean glycemia showed to be significantly better controlled in the experimental group than in the control group after 6 months ($p = 0.002$). Table 2 shows a continuous trend of improvement of mean glycemia in the experimental group, contrasted to the control group's only temporary improvement.

A statistically significant decrease in the number of hyperglycemic events per patient per day was observed in the experimental group after 6 months ($p = 0.022$) (Table 4). Also, there was a decrease in the number of hypoglycemic events after 6 months, although it did not reach a statistically significant level ($p = 0.223$) (Table 4). In the control group there was an improvement in the average number of hypoglycemia per patient both after 3 and 6 months compared to the baseline, albeit it was not statistically significant (Table 4). A significant decrease in the average number of hyperglycemia per patient was found in the control group after 3 months ($p = 0.017$), but not after 6 months ($p = 0.828$) (Table 4).

still, the advantage over the intensive classic method (intensive self-monitoring) is not straightforward. Specifically, the improvement in average HbA1c levels was observed in both groups and the difference between them was neither clinically nor statistically significant (1.4% drop in the experimental and 1.3% in the control group). Yet, other clinically important outcomes measured (namely mean glucose levels, number of hypoglycemic and hyperglycemic events) showed higher treatment effects in the experimental group in the long run. We propose some explanations for such ambiguous results.

Firstly, all our participants had relatively high average HbA1c levels (≥ 8%), with one-third of them having values over 10% at some point of the study. The earlier-mentioned low correlation between mean glycemia and HbA1c can be thus ascribed to the restricted range of the scores; the effect of which is a reduced correlation when compared to its magnitude observed in whole population. Therefore, these two measures cannot be seen as interchangeable in assessing glycemic states in our sample. Furthermore, due to the relative protractedness of HbA1c (HbA1c known to be influenced by glycemic levels of up to four months before the measurement [12, 13]) we are inclined to believe that mean glucose levels are more appropriate measures in detecting fine and more recent changes in glycemic levels in a highly event-dynamic sample as was ours. In other words, it is possible that HbA1c was not sensitive enough to detect the changes in the control group in the last three months of the trial, and, as a result, we obtained no statistically significant differences with regard to HbA1c, which was in contrast to other relevant findings.

We also suspect that short-term improvements in the control group in the first three months could be caused by the so-called "experimental effect" which the study had on the participants. In particular, it seems reasonable that "reactivity of measurement" [14] phenomenon had taken place; namely, thanks to the frequent intensive SMBG measurements at the

Table 4

Average number of hypo- and hyperglycemic events per day*

Period of the study	Hypoglycemia			Hyperglycemia		
	Experimental group	Control group	$p^{\dagger}$	Experimental group	Control group	$p^{\dagger}$
Baseline	0.8 ± 0.7	0.7 ± 1.4	0.015	4.3 ± 1.7	3.6 ± 2.1	0.266
3 months	0.6 ± 0.7	0.5 ± 0.6	0.429	3.6 ± 2.1	3.0 ± 1.9	0.910
6 months	0.6 ± 0.6	0.6 ± 1.4	0.468	3.2 ± 1.6	3.6 ± 2.3	0.115
$p\ \Delta(1\text{-}2)^{\ddagger}$	0.180	0.715		0.089	0.017	
$p\ \Delta(1\text{-}3)^{\ddagger}$	0.223	0.175		0.022	0.828	

***The results are presented as mean ± standard deviation obtained from 27 measures per visit (9 capillary glycemic tests × 3 days) per individual. Hypoglycemia defined as blood glucose < 3.5 mmol/L; hyperglycemia as blood glucose > 10.0 mmol/L. †Wilcoxon-Mann-Whitney test (between-subjects effects) controlled for baseline differences. ‡Wilcoxon signed-ranks test (within-subjects effects) examining changes from the baseline levels.**
Δ (1-2) – difference in average number of events per day between baseline and 3-month measurement; Δ (1-3) – difference in average number of events per day between baseline and 6-month measurement

Discussion

The results of this six-month long study suggest that even a short-term use of the CGMS method influences therapy decisions and subsequently leads to the improvement of metabolic control in young T1DM patients in the long run; baseline the participants might have changed their health-related behaviors, but the benefits of it faded out in the course of time. On the contrary, the group receiving treatment and accompanying advice on the basis of their CGMS measures persisted in showing improvements in all outcomes (quite the opposite to what Yates et al. [15] found) throughout

the study, which might indicate profound changes in treatment adherence.

Indeed, further empirical investigation is required to prove the aforementioned hypothesis, even though psychological effects on diabetes treatment adherence when monitoring blood glucose levels with memory-equipped devices have already been discussed [16, 17]. Although the experts emphasize the potential benefits of those devices, some concern was over the possible information overload for the patients [17]. With regard to this, we believe the overload would be less of an issue when the CGMS is used for a short-term only and under medical supervision, as was the case in our study. It must be stated, however, that our intention was not to imply that three-day use would be its suggested use; rather we merely tested whether short-term application of the CGMS could be of any value for clinical practice.

Conclusion

A significant reduction of mean glycemia and hyperglycemic events compared to the control group, accompanied with the observed reduction of HbA1c levels and the number of hypoglycemic events does lead us to a conclusion that the CGMS is a valuable add-on in the control of type 1 diabetes in young patients, even when used for such a brief period. It represents a newer methodology that seems to be better accepted by both younger patients and their parents since it produces comprehensible graphic-imaging of glycemia dynamics, which at least in theory, should lead to better patient's and parents' compliance with the therapy. From the practitioner's perspective, we found that the CGMS offers more information and allow for better decisions in the course of therapy, especially with regard to the insulin administration (dosage and timing) which plays a crucial role in glycemic control. Still, more research is needed in order to determine optimal parameters of CGMS use to exploit it in the most effective way. Lastly, it seems that intensified (e.g. 9-point) self-monitoring of blood glucose has its benefits as well and that at this stage of research it can be perceived as a second-choice alternative to the CGMS, especially in economically challenged countries, such as Bosnia & Herzegovina, where affording continuous glucose measuring devices could still represent an issue.

R E F E R E N C E S

1. *The Diabetes Control and Complications Trial Research Group.*The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus N Engl J Med 1993; 329(14): 977–86.
2. *Davis EA, Keating B, Byrne GC, Russell M, Jones TW*. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. Diabetes Care 1997; 20(1): 22–5.
3. *Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV*. Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care 2001; 24(11): 1858–62.
4. *Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P.* A pilot study of the continuous glucose monitoring system: clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. Diabetes Care 2001; 24(12): 2030–4.
5. *Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R,* et al. Continuous subcutaneous glucose monitoring in children with type 1 diabetes. Pediatrics 2001; 107(2): 222–6.
6. *Fiallo-Scharer R.* Diabetes Research in Children Network Study Group. Eight-point glucose testing versus the continuous glucose monitoring system in evaluation of glycemic control in type 1 diabetes. J Clin Endocrinol Metab 2005; 90(6): 3387–91.
7. *Lagarde WH, Barrows FP, Davenport ML, Kang M, Guess HA, Calikoglu AS*. Continuous subcutaneous glucose monitoring in children with type 1 diabetes mellitus: a single-blind, randomized, controlled trial. Pediatr Diabetes 2006; 7(3): 159–64.
8. *Tanenberg R, Bode B, Lane W, Levetan C, Mestman J, Harmel AP,* et al. Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. Mayo Clin Proc 2004; 79(12): 1521–6.
9. *Ludvigsson J, Hanas R.* Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. Pediatrics 2003; 111(5 Pt 1): 933–8.
10. *Schaepelynck-Bélicar P, Vague P, Simonin G, Lassmann-Vague V*. Improved metabolic control in diabetic adolescents using the continuous glucose monitoring system (CGMS). Diabetes Metab 2003; 29(6): 608–12.
11. *Deiss D, Bolinder J, Riveline JP, Battelino T, Bosi E, Tubiana-Rufi N,* et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 2006; 29(12): 2730–2.
12. *Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE*. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes Care 2002; 25(2): 275–8.
13. *Kilpatrick ES*. Haemoglobin A1c in the diagnosis and monitoring of diabetes mellitus. J Clin Pathol 2008; 61(9): 977–82.
14. *Becker H, Roberts G, Voelmeck W*. Explanations for improvement in both experimental and control groups. West J Nurs Res 2003; 25(6): 746–55.
15. *Yates K, Hasnat Milton A, Dear K, Ambler G.* Continuous glucose monitoring-guided insulin adjustment in children and adolescents on near-physiological insulin regimens: a randomized controlled trial. Diabetes Care 2006; 29(7): 1512–7.
16. *Wysocki T.* Behavioral assessment and intervention in pediatric diabetes. Behav Modif 2006; 30(1): 72–92.
17. *Diabetes Research in Children Network (DirecNet) Study Group.* Psychological aspects of continuous glucose monitoring in pediatric type 1 diabetes. Pediatr Diabetes 2006; 7(1): 32–8.

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