BENEFITS OF THREE-MONTH CONTINUOUS GLUCOSE MONITORING FOR PERSONS WITH DIABETES USING INSULIN PUMPS AND SENSORS

Karolina Peterson^a, Jana Zapletalova^b, Pavla Kudlova^c, Veronika Matuskova^a,
Josef Bartek^d, Dalibor Novotny^e, Rudolf Chlup^{a, f}

^a Department of Physiology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

^b Department of Biophysics, Faculty of Medicine and Dentistry, Palacky University Olomouc

^c Department of Nursing, Faculty of Medicine and Dentistry, Palacky University Olomouc

^d Department of Medical Chemistry and Biochemistry, Faculty of Medicine and Dentistry, Palacky University Olomouc

^e Department of Clinical Biochemistry, University Hospital, Olomouc

^f Department of Internal Medicine II, University Hospital Olomouc, I. P. Pavlova 6, 775 20 Olomouc

e-mail: karolinapeterson@yahoo.com

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Background: The latest Paradigm 722 insulin pump, Medtronic MiniMed, USA, enables daily reading of 288 interstitial fluid glucose concentrations determined by a sensor inserted into subcutaneous tissue; the sensor signals are transmitted into the insulin pump, enabling the patient to see real-time glucose concentration on the display and adapt further treatment.

Aims: To assess the evolution of HbA1c over the course of a 3-month period in two cohorts of persons with type 1 (n=39) or type 2 (n=3) diabetes (PWD): 1) PWD on Paradigm 722 using sensors for continuous glucose monitoring (CGM group), 2) PWD on other types of insulin pumps performing intensive self-monitoring as before (3 to 6 times/d) on glucometer Linus, Wellion, Agamatrix (control group).

Methods: Compliant PWDs using insulin pump with insulin aspart for several previous months were included in the study. Seventeen were put on Paradigm 722 with CGM and 25 were included in the control group. Paired t-test and the statistical program SPSS v.15.0 were used to analyze the data.

Results: There was no significant difference in age between the two groups ($P=0.996$), in diabetes duration ($P=0.482$) or in daily insulin dose ($P=0.469$). In the CGM group (but not in the control group) HbA1c/IFCC dropped from $6.98 \pm 0.43\%$ to $5.98 \pm 0.36\%$ ($P=0.006$) within 1 month and remained reduced.

Conclusion: The use of the Paradigm 722 insulin pump with CGM resulted in significant improvement in HbA1c which appeared within one month and remained throughout the whole 3-month study period. No significant improvement in HbA1c was seen in the control group.

INTRODUCTION

In persons with diabetes (PWD) self-monitoring of the concentration of glucose in plasma (SMPG) is a basic means of preserving compensation^{1,2}. The emergence of test strips and glucometers in the last 30 years has enabled the glucose concentration self-monitoring and this has gradually replaced the relatively inaccurate and inconvenient measurement of glucose in urine³⁻¹³.

A large amount of attention is given to the frequency of self-monitoring and its effectiveness¹⁴⁻¹⁶. In 1993, the well known study DCCT (Diabetes Control and Complications Trial) emphasized that in PWD1 SMPG should be performed at least four times daily and subsequently corrected with intensive insulin therapy^{17, 18}. Currently it is recommended that people with diabetes mellitus type 1 check their glycemia 5 to 8 times per day, and persons with type 2 diabetes at least 3 times daily. Intensive self-monitoring is of particular importance in PWD on continuous subcutaneous insulin infusion.

Continuous glucose monitoring with transcutaneous sensors used since 2000 offers new possibilities^{19, 20}. The latest Paradigm 722 insulin pump, Medtronic MiniMed, Northridge, CA, USA, enables daily reading of 288 interstitial fluid glucose concentrations determined by a sensor inserted into subcutaneous tissue; the sensor signals are transmitted wirelessly into the insulin pump at 5-minute intervals, enabling the person to see his/her real-time glucose concentration on the pump display and modify further treatment.

The sensor is indicated for single use and as a rule works well after a period of seven or more days following introduction²¹. The concentration of glucose in the interstitium (ISFG) correlates highly with P-glucose (PG). Recently, we have demonstrated a high correlation between average ISFG and HbA1c²². So far, however, it is not entirely clear what the contribution of CGM is to the development of HbA1c, or to what extent HbA1c interacts with the variability in glycemia and other factors²³.

AIM

To demonstrate the development of HbA1c in PWD on insulin pumps 1) in a group of subjects using conventional self-monitoring and 2) in a separate group of subjects using continuous monitoring.

MATERIAL AND METHODS

Subjects

Two independent cohorts (groups) of persons with type 1 (n=39) or type 2 (n=3) diabetes were followed:

1. Control group of 25 persons with diabetes (13 men, 12 women; aged 24-66 years; duration of diabetes 2-43 years) treated with an insulin analogue aspart using MiniMed 508 or Paradigm 712 or Paradigm X22 insulin pumps without a sensor, Medtronic Minimed; subjects provided SMPG similarly as before.
2. Intervention group of 17 persons with diabetes (11 men, 6 women, aged 19-69 years; duration of diabetes 1-45 years) who applied insulin analogue aspart Paradigm 722 insulin pumps, Medtronic Minimed, in whom CGM was conducted for the course of 3 months with transcutaneous sensors. This monitoring replaced the previous SMPG done before the study started. The first sensor was inserted at the beginning of the trial under professional supervision into the subcutaneous tissue of the gluteal region or abdomen, other sensors were inserted by the subject him/herself at home. Each sensor was left in the subcutaneous tissue until it stopped working (usually 7-14 days).

All subjects signed informed consent. The study was approved by the local ethics committee. All procedures were performed in accordance with the Helsinki Declaration of 1973 as revised in 2000.

Design of the study

This prospective non-randomised pilot study took place between 2007 and 2008 at the Faculty of Medicine and Dentistry, Palacky University Olomouc and at the University Hospital, Olomouc, Czech Republic.

All PWD were monitored on an out-patient basis for the period of three months. At the beginning of the study and at the end of each month, clinical and laboratory (HbA1c) examinations were performed.

Education and re-education of the subjects was aimed at the insertion of the CGM sensor, handling the transmitter and pump and at the adaptation of prandial insulin boluses according to the glycemic values and real-time status.

Self-monitoring in the control group and sensor calibration in the intervention group were carried out using glucometr Linus, Wellion, Agamatrix, Salem, NH, USA. Frequency of SMPG was assessed using Diabass 4 software.

In the CGM group, the frequency of readings of PG was assessed using professional Solutions software, Medtronic Minimed, Northridge, CA, USA.

Calibration of sensors was implemented according to the manufacturer's recommendations twice daily in 12-hour intervals with a Linus glucometer.

Determination of Haemoglobin A1c

The HbA1c concentration in blood was determined using the sophisticated HPLC procedure in the Department of Clinical Biochemistry, Teaching Hospital Olomouc. The analyzer PDQ Plus employs the principles of boronate affinity and high-performance liquid chromatography (HPLC). Glycated proteins (haemoglobins and plasma proteins) differ from non-glycated proteins by the attachment of sugar moiety to the former at various binding sites by means of a ketoamine bond. GHb and GPP thus contain 1,2-cis-diol groups not found in non-glycated proteins. These diol groups provide the basis for separation of glycated and non-glycated components by boronate affinity chromatography. In this analytical technique, a boronate is bonded to the surface of the column support. When a solution of proteins is passed through the column, the glycated component is retained by complexing its diol groups with the boronate. After the unretained non-glycated component elutes from the column, the glycated component is eluted from the column with a reagent that displaces it from the boronate. Both components are detected spectrophotometrically at 413 ± 2 nm. Reference range for normal population: 2.8 to 4.0 % (IFCC scale). The conversion to traditional NGSP/DCCT scale may be performed using the formula $IFCC [\%] = (DCCT - 2.15)/0.915$. Parameters of reliability: limit of quantitation 3.0 %, linearity: up to 1.5 %; repeatability (within-run imprecision): 1.4 %; reproducibility (between-run imprecision): 1.4 %.

Statistical analysis

The program SPSS v.15.0, SPSS, Inc., Chicago, IL, USA was used for statistical analysis.

The following tests were applied to evaluate the data: the chi-squared test (sex distribution in each group), two-sample t-test, (differences in age at diabetes diagnosis, differences in duration of diabetes and in duration of insulin pump treatment, differences in HbA1c values between the control and intervention group at baseline and in control visits, differences in age at the time of enrolment into the study and differences in insulin doses between the control and intervention group), paired samples t-test in the intervention and control group (comparison of HbA1c between control visits 1, 2, 3 and at baseline). $P < 0.05$ was considered significant.

RESULTS

There were no significant differences found between groups in the following parameters: age at diabetes diagnosis, age at inclusion into the study, male/female ratio in both groups, duration of the insulin pump therapy and daily insulin dose (Table 1). The frequency of self-monitoring in SMPG group was 3 to 6 plasma glucose

Table 1. Characteristics of the control (SMPG) group and of the intervention (CGM) group.

Group	SMPG	CGM	Significance (P)
N	25	17	N/A
M/F	13/12	11/6	0.414
Age (mean±SE) [years]	44.9±2.6	44.9±4.0	0.996
Age range [years]	24 - 66	19 - 69	N/A
Duration of diabetes (mean±SE) [years]	15.4±2.0	17.8±2.9	0.482
Duration of diabetes range [years]	2-43	1-45	N/A

N/A not applicable

Table 2. HbA1c and insulin doses in the control (SMPG) group and the intervention (CGM) group (mean±SE).

Group	SMPG				CGM			
Month	Start	1	2	3	Start	1	2	3
HbA1c/IFCC [%]	7.26 ± 0.31 n=25	7.32 ± 0.43 n=23	7.71 ± 0.39 n=25	7.63 ± 0.41 n=24	6.98 ± 0.43 n=17	5.98 ± 0.45 n=17	5.96 ± 0.45 n=17	6.17 ± 0.36 n=17
Insulin aspart [i.u./d]	38.05 ±2.47 n=20	-	-	38.48 ±2.67 n=21	41 ±4 n=14	-	-	43.13 ±4.18 n=15

Fig. 1. Boxgraph (medians, quartils): The evolution of HbA1c during three-month follow-up in the control (SMPG) group; P – significance vs. baseline. **Fig. 2.** Boxgraph (medians, quartils): The evolution of HbA1c during three-month follow-up in the intervention (CGM) group; P – significance vs. baseline.

estimations per day. In the intervention group the CGM was carried out in approximately in 90 % of time of the study period.

The change of HbA1c during the three-month observation was not significant in the control group (Fig. 1). Contrary to these results, the HbA1c in the intervention

group which used continuous self-monitoring decreased by the end of 1st month and this reduction continued during the control visits of the second and third months (Fig. 2, Table 2).

There was no difference ($P=0.597$) in values of HbA1c between the control group and the intervention group at

baseline. However, significant differences in HbA1c were found at the end of the first month ($P=0.041$), at the end of the second month ($P=0.006$) and at the end of the third month ($P=0.016$). There was no significant change in daily dose of insulin in either group.

DISCUSSION

Continuous subcutaneous infusion with an insulin pump is one of the most effective methods of treatment in persons with diabetes^{2, 24}. Insulin pumps lead not only to the improved glycemic profiles but in comparison with conventional medications, also limit the degree of hypoglycemia²³. In our recent study we concluded that for this form of treatment, it is better to give priority to short duration insulin analogues (such as insulin aspart, Novorapid) than human insulin Actrapid²⁵. This discovery is in accordance with other investigations which have confirmed the superior efficacy of the Lispro insulin analog in external pumps (Humalog)²⁶.

Continuous glucose monitoring (CGM) during insulin pump therapy appears to be an excellent alternative for further improvement of metabolic compensation²⁷⁻³². The advantage of this compensation control is that it enables the patient to register both average 24-hour glycemia and variability in glycemia. The relationship between the glycemia and HbA1c development is being investigated³³⁻³⁵. There is intense research on working out the principles for using CGM. For a rational use of CGM, the financial and educational resources diabetes centres need to be increased so that persons with diabetes can use CGM monitoring appropriately and react to the changing glycemia^{19, 36, 37}.

Continuous glucose monitoring is accurate enough for both type 1 and type 2 diabetes mellitus. It is safe and well-tolerated. Its numerical results are comparable with the results of SMPG obtained using glucometers^{21, 38-40}. The outcome of our study has shown that the clinical effects of CGM are clearly better than those of SMPG: continuous glucose monitoring leads to decrease in HbA1c as early as the end of the first month. Different statistical analytical tests also show the positive clinical effects of CGM on metabolic compensation³². We observed no local or systemic complications of the sensor use during the whole period of its function which usually ranged between 7 and 14 days. This is also in accordance with the findings of others⁴¹. CGM proved to be valuable in all age groups when used on a regular basis⁴². Aside from the assessment of metabolic control in persons with type 1 diabetes, CGM may be applied also in other specific areas, such as in calculation of premeal insulin boluses in persons with type 1 diabetes mellitus⁴³ and in glycemic index determination^{44, 45}. Further studies are necessary to evaluate more precisely the influence of glycemic variability and frequency of hypo- and hyperglycemia on HbA1c.

CONCLUSION

Using conventional self-monitoring (3-6 measurements per day) we found no substantial change in HbA1c within 3 months. With the continuous self-monitoring used for 90 % total time the HbA1c decreased about 1 % within the first month and this improvement remained for the rest of the three-month observation. Continuous self-monitoring with transcutaneous sensors appears to be an important measure for improving metabolic compensation in persons with diabetes, and the results are better than the results for SMPG. We conclude that continuous self-monitoring could and should become a regular part of treatment of selected persons with diabetes. This will require adequate financial measures and, education of the healthcare providers and all members of the diabetes team.

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