

## CLINICAL PERFORMANCE OF CONTINUOUS GLUCOSE MONITORING SYSTEM IN TYPE 1 DIABETICS

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*Key words: glucose monitoring, evaluation, type 1 diabetes*

### SUMMARY

*The aim of the study was to determine whether a 3-day glucose profile is sufficiently representative of the overall metabolic control of a patient, and to evaluate clinical performance of the continuous glucose monitoring system (CGMS) in type 1 diabetic patients. Eighteen type 1 diabetics (male 7, female 11, mean age  $26.7 \pm 4.6$  years) were included in the study performed at Outpatient Clinic of University Department of Endocrinology, Diabetes and Metabolic Disorders in Skopje. The patient mean  $HbA_{1c}$  was  $8.7 \pm 1.6\%$ . All patients were treated with intensive insulin therapy (4 daily injections). CGMS (Minimed CGMS gold) was performed for 72 hours. Results were discussed with the patients and insulin treatment was adjusted. Two months later  $HbA_{1c}$  was determined. CGMS profiles verified blood glucose excursions unrecognized by self-monitoring measurements in all patients. A mean of  $0.9 \pm 1.2$  asymptomatic nocturnal hypoglycemic events per patient was recorded with CGMS during the night and early morning. Glucose period exceeding  $22.2$  mmol/L due to hypoglycemic event was recorded in six patients. Prolonged periods of hyperglycemia (blood glucose values  $>14$  mmol/L for 5 hours) were recorded in eight*

*patients. Dawn phenomenon (elevation in glucose level during the early morning) was found in four patients. The 3-day glucose profile obtained by CGMS was found to be representative of the overall metabolic control in a particular patient. CGMS is easy to perform and in our study resulted in  $HbA_{1c}$  improvement at 2 months.*

### INTRODUCTION

The major objective in the treatment of patients with diabetes mellitus (DM) type 1 is to maintain blood glucose levels near to the normal values and to obtain levels of  $HbA_{1c}$  close to 7%. Self-monitoring of blood glucose (SMBG) is very important in the management of diabetes. The American Diabetes Association suggests that patients with DM type 1 measure their blood glucose at least three or more times daily (1). Yet, SMBG is inadequate, as it provides only a partial and incomplete picture of circadian blood glucose fluctuations. Frequent SMBG is often not accepted by the patients because it is invasive and painful. Prospective randomized clinical trials such as the Diabetes Control and Complications Trial (DCCT) (2) and U.K. Prospective Diabetes Study (UKPDS) (3) have shown that improved glycemic control is associated with sustained decreased rates of retinopathy, nephropathy, and neuropathy. The results of these studies have demonstrated that intensive

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insulin therapy was associated with a threefold increase in the occurrence of severe hypoglycemia (4). The recent availability of a home continuous glucose monitoring system (CGMS) represents an important advance in the management of subjects with DM type 1 (5). The CGMS is manufactured by Medtronic-Minimed, which covers the demands of intensive insulin therapy with intensive monitoring of blood glucose levels (6).

The performance of CGMS was previously evaluated against blood glucose measurements obtained using patient home blood glucose meter readings according to the manufacturer's criteria (7), however, only limited experimental data are available on CGMS performance compared with plasma glucose determinations using the more accurate glucose oxidase method for blood glucose determination (8). The CGMS is a holter-style sensor system and continuously monitors (every 5 minutes, 288 measurements daily) interstitial glucose levels. It consists of four components: 1) a pager-sized glucose monitor, 2) a sterile disposable subcutaneous glucose sensor, 3) a cable that connects the sensor to the monitor, and 4) a com-station that enables data stored in the monitor to be downloaded to a computer (Fig.1). The glucose sensor is inserted in the abdominal subcutaneous tissue, and it converts the measured interstitial glucose levels into electrical current (based on enzyme glucose oxide). CGMS is designed to provide continuous glucose measurements in the range of 2.2-22.2 mmol/L for up to 72 hours (5).

Figure 1. A holter-style CGMS in pager size



The initial studies on the CGMS were performed in adult subjects (9). These studies showed the system to be well tolerated by adult patients with DM type 1. Additional research has shown that the information obtained allows the patient and health care team to adjust the timing and dosage of insulin and the meal plan to improve glycemic control, resulting in an average HbA<sub>1c</sub> decrease from 9.9% to 8.8% after 5 weeks (6). Chase *et al.* (10) studied continuous glucose monitoring in pediatric patients to determine whether it could help recognize nocturnal hypoglycemia or lower HbA<sub>1c</sub>. Another study in 11 patients with DM type 1 showed a HbA<sub>1c</sub> decrease by  $0.36 \pm 0.07\%$  in the CGMS group *vs.*  $0.2 \pm 0.2\%$  in the control group.

There is no published information on the use of CGMS in adult patients with DM type 1 in the Republic of Macedonia. This is the first study in our country of clinical performance of CGMS in patients with DM type 1 on intensive insulin therapy (multiple daily insulin injection).

### *Aim of the study*

The aims of the study were:

- to determine whether a 3-day glucose profile is sufficiently representative of the patient overall metabolic control;
- to determine whether it is possible to reduce HbA<sub>1c</sub> levels with the modifications suggested by CGMS; and
- to evaluate clinical performance of CGMS as a routine method for DM type 1 outpatients at our Department.

## PATIENTS AND METHODS

### *Patient selection*

Eighteen patients with DM type 1 were recruited for the study at University Department of Endocrinology, Diabetes and Metabolic Disorders, in Skopje, Macedonia. The study was performed from February 2003 to May 2004. Inclusion criteria were HbA<sub>1c</sub> values >8.0% associated with one of the following clinical problems: elevated fasting blood glucose levels or suspected dawn phenomenon; glycemic excursion with exercise; insulin dosage >1–1.5 units/kg/day; patients

with widely fluctuating blood glucose levels or recurrent hypoglycemia, hypoglycemia unawareness, or suspected nocturnal hypoglycemia combined with an HbA<sub>1c</sub> level <8.0% were also eligible. After initial explanation what a 3-day sensor-wear entailed, all subjects agreed to wear the sensor for a 3-day period. All patients agreed to participate and signed an informed consent. The mean age of the subjects was 26.7±4.6 years. There were 7 male and 11 female patients. The patients had a mean duration of diabetes of 6.7±4.2 years and a mean HbA<sub>1c</sub> of 8.7±1.6% before CGMS. All patients took three to four insulin injections *per* day (three times short or rapid acting insulin and one time evening intermediate insulin).

## Methods

All patients were instructed on the use of the CGMS device and were asked to enter at least four daily SMBG measurements into the instrument for calibration. One-hour training session on the use of CGMS was performed in each patient. After the insertion and initial calibration, patients were asked to keep detailed written records of any particular event (insulin dose, food intake, physical activity, etc.) and to enter these events into the monitor during their routine daily activities (outpatients). The system was well tolerated by all patients. After 3 days, the patients came back to the Outpatient Clinic, the data were downloaded *via* Com-Station using the MiniMed Solutions Software version 2.0b (MiniMed, Sylmar, CA). The following figures of glucose periods were analyzed:

- glucose periods <2.2 mmol/L
- glucose periods >22.2 mmol/L
- rapid glycemic excursions (increase or decrease of glucose values >11 mmol/L over 3-4 hours)
- prolonged period of hyperglycemia (blood glucose values >14 mmol/L for 5 hours)
- preprandial and postprandial (2 hours) glucose levels on each main meal (breakfast, lunch and dinner)

The records from the CGMS were analyzed together with the patients. After the analyses, specific recommendations were given to each patient:

- change in short or rapid acting insulin

- change in intermediate insulin (morning or evening)
- change in treatment of hypoglycemia
- night-time change because of the dawn phenomenon
- modification of regimen for glycemic food
- alteration in the physical activity approach

HbA<sub>1c</sub> was measured by high-performance liquid chromatography (normal range 3.8%-5.8%) before entering the study and 2 months after wearing the CGMS.

## Statistical analysis

Statistical analyses were made using the Statistica v 2.0 software. Student's t-test was used for mean values of HbA<sub>1c</sub>. All results nominally significant at p<0.05 were indicated.

## RESULTS

The CGMS was well tolerated by all patients. The mean duration of sensor-wear was 71.3±10.4 hours. A total of 36±8 events (meal, exercise, physical activity) *per* patient were entered in the monitor during CGMS use. In the logbooks, there were 12.6±5 SMBG measurements during the three-day wearing of CGMS. A mean of 0.9±1.2 asymptomatic nocturnal hypoglycemic events *per* patient were recorded with CGMS during the night and early morning. Glucose periods over 22.2 mmol/L due to hypoglycemic events were recorded in six patients. Prolonged periods of hyperglycemia (blood glucose values >14 mmol/L for 5 hours) were recorded in eight patients. Four patients were found to have dawn phenomenon (glucose elevation in the early morning). Preprandial glucose measurements with CGMS showed seven patients to have high breakfast pattern, high lunch pattern and high dinner pattern were observed in six patients each, one patient had low breakfast pattern, two had low lunch pattern and four had low dinner pattern. There were no low postprandial patterns. Ten patients had high postbreakfast pattern, nine had high postlunch pattern and seven had high postdinner pattern (Table 1).

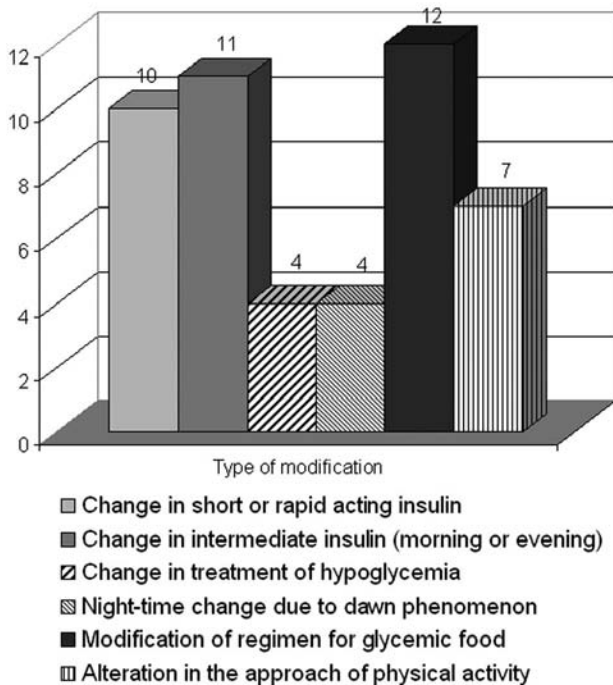
The modification in diabetes treatment was performed after the wear of CGMS. A modification of short or rapid acting insulin was made in ten patients,

Table 1. Number of preprandial and postprandial patterns in patients after three-day CGMS

	Preprandial	Postprandial
<i>Breakfast</i>		
Low	1	/
High	7	10
<i>Lunch</i>		
Low	2	/
High	6	9
<i>Dinner</i>		
Low	4	/
High	6	7

and of intermediate insulin in 11 patients (morning basal insulin was recommended in six patients). Change in the treatment of hypoglycemia was made in four patients and night-time change due to dawn phenomenon in four patients. A modification of the glycemic food regimen was made in twelve patients, and of the physical activity approach in seven patients. There was a mean of  $2.7 \pm 0.7$  recommendations *per* patient (Fig.2).

Figure 2. Type and number of modifications in diabetes treatment



A significant HbA<sub>1c</sub> decrease by 0.9% was observed after two months of wearing the CGMS ( $8.7 \pm 1.6\%$  vs.  $7.8 \pm 1.2\%$ ,  $p < 0.05$ ).

## DISCUSSION

CGMS has opened a new window in the glycemic profile, allowing for a direct insight into the glycemia pattern in particular patients and showing predictable and unpredictable events that cannot be indicated by SBMG. The recommendations for adjustment of diabetes regimen based on CGMS data reduced the number of high preprandial and postprandial patterns and HbA<sub>1c</sub> level.

Nocturnal hypoglycemia and dawn phenomenon are frequently found but are not apparent with finger-stick monitoring alone because finger-sticks are rarely done at that time of day (11). In our patients, the CGMS confirmed what has been described in previous studies, which showed asymptomatic nocturnal hypoglycemia in patients who measured night-time blood glucose levels (12,13).

The CGMS data also showed the occurrence of hypoglycemia associated with exercise in our patients. Some patients experienced hyperglycemia after the completion of exercise as the result of excess carbohydrate ingestion at the time of hypoglycemia.

## CONCLUSION

It is concluded that a 3-day glucose profile obtained by CGMS is representative of the overall metabolic control of the patient. Following the instructions and recommendations concerning CGMS glucose data, there was an improvement of HbA<sub>1c</sub> in our study. CGMS is easy to perform, is well tolerated by the patients, and could be used as a routine method at outpatient clinics to improve the overall metabolic control. Further studies with the CGMS in larger series of patients are needed to support these findings.

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