The Continuous Glucose Monitoring System Is Useful for Detecting Unrecognized Hypoglycemias in Patients With Type 1 and Type 2 Diabetes but Is Not Better Than Frequent Capillary Glucose Measurements for Improving Metabolic Control

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OBJECTIVE — To evaluate whether the continuous glucose monitoring system (CGMS; MiniMed, Sylmar, CA) is useful for investigating the incidence of unrecognized hypoglycemias in type 1 and type 2 diabetic patients and for improving metabolic control in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 70 diabetic subjects (40 type 1 and 30 type 2 subjects) were monitored using the CGMS. The number of unrecognized hypoglycemias was registered. Furthermore, the 40 type 1 diabetic patients whose treatment was modified in accordance with the information obtained from the CGMS were compared with a control group of 35 different type 1 diabetic patients using intensive capillary glucose measurements. HbA_{1c} levels were measured before the monitoring period and 3 months later.

RESULTS — The CGMS detected unrecognized hypoglycemias in 62.5% of the type 1 diabetic patients and in 46.6% of the type 2 diabetic patients. We found that 73.7% of all events occurred at night. HbA_{1c} concentrations decreased significantly in both the group of type 1 diabetic subjects monitored with the CGMS (from 8.3 ± 1.6 to $7.5 \pm 1.2\%$, $P < 0.01$) and the control group (from 8.0 ± 1.4 to $7.5 \pm 0.8\%$, $P < 0.01$). The greatest reduction was observed in the subgroup of patients who started continuous subcutaneous insulin infusion therapy, both in the CGMS-monitored and control groups (from 9.4 ± 2 to $7.2 \pm 1.4\%$ and from 8.1 ± 1.8 to $7.1 \pm 0.6\%$, respectively).

CONCLUSIONS — The CGMS is useful for detecting unrecognized hypoglycemias in type 1 and type 2 diabetic subjects; however, it is not better than standard capillary glucose measurements for improving metabolic control of type 1 diabetic subjects, regardless of the therapeutic regimen.

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S ome relevant prospective studies have demonstrated that good metabolic control of diabetes decreases the risk of chronic complications (1,2). Intensive therapeutic regimens with multiple insulin injections (MIIs) combined with frequent measurements of capillary blood glucose levels are known to be the most useful ways of achieving good metabolic control. It is also known that intensive regimens can increase the number of hypoglycemias and that the perception of autonomic symptomatology may decrease over time.

It is often difficult to achieve optimal control (3,4), despite intensive insulin therapy and frequent self-monitoring of blood glucose, partly because of the limitations of the glycemic profile obtained from intermittent fingersticks (5). A new Holter-style sensor system recently came on the market (continuous glucose monitoring system [CGMS]; MiniMed) for continuously measuring glucose concentrations in subcutaneous tissue (6). This system has been validated by several reports (7,8) and has been shown to provide a good correlation between blood and interstitial glucose levels (9–11). The continuous glucose profile obtained using this system is easy for physicians to interpret, thus patient treatment can be modified and glucose control improved. Recent studies have shown a significant decrease in HbA_{1c} in patients monitored with the CGMS with subsequent treatment modifications (12–15); however, the lack of an adequate control group casts doubt on the results of such studies.

Although a high incidence of unrecognized hypoglycemias has been detected using the CGMS in patients with type 1 diabetes (16), extensive information about these events in type 2 diabetic subjects is not available. The potential danger of these unrecognized hypoglycemias makes their detection and prevention one of the main objectives of control in diabetic patients. In this regard, the CGMS may be a useful tool for early detection of asymptomatic hypoglycemias, but little

information has been published on the technical problems involved in practical CGMS use.

The three main objectives of this study are to investigate whether the CGMS is more useful than frequent capillary glucose measurements with a view to modifying treatment and improving metabolic control of type 1 diabetic subjects, to evaluate the incidence of unrecognized hypoglycemias in type 1 and type 2 diabetic patients, and to evaluate the actual incidence of technical problems related to CGMS use.

RESEARCH DESIGN AND METHODS

— A total of 105 diabetic patients (75 with type 1 diabetes, 30 with type 2 diabetes) were included in the study. Type 1 diabetic patients with inadequate metabolic control were randomly assigned to either the group to be monitored with the CGMS ($n = 40$) or the control group ($n = 35$), using frequent capillary glucose measurements. The CGMS group was monitored for 3 days using the CGMS, and the information obtained was used to modify treatment. Glucose data from each day were analyzed at five different times: between breakfast and lunch, between lunch and dinner, between dinner and bedtime, from bedtime to 4:00 A.M., and between 4:00 A.M. and breakfast. Responses to hypoglycemia and exercise and the presence of unrecognized hypoglycemias were also evaluated. The control group members' treatment was modified using the information obtained from capillary glucose measurements (at least eight measurements per day for 3 days: before each meal, 2 h after meals, at bedtime, and at 4:00 A.M.).

All patients were evaluated by the clinician between two and four times over the following 2–3 months after therapy modifications had been made. Diet, treatment of hypoglycemia, and exercise were also revised individually by the nurse during three to four sessions.

The CGMS was inserted in all monitored subjects by the same specialized nurse. Patients were encouraged to continue with their regular lifestyle and treatment during the monitoring period and were instructed to enter glucose meter values (at least four a day) and the times of key events (meals, exercise, hypoglycemias, insulin doses, or oral drug intake) into the monitor. The patients recorded all these events and other information

they considered relevant in a logbook. Patients always used the same brand of glucometer during the monitoring period. The patients were given a 24-h contact telephone to ask questions or solve problems related to CGMS use. At 3 days after insertion, the patients came back to the clinic with their logbook to have the CGMS removed. Data were downloaded to the computer and evaluated by the clinician. The patients included in the control group also used a logbook to record information about meals, exercise, and other matters that could potentially affect glucose levels during the 3 days of intensive glucose measurements. HbA_{1c} levels were measured with the DCA 2000 system (reference interval of 3–6%; Bayer, Tarrytown, NY) before the monitoring period and 3 months after therapeutic modifications were made.

The frequency of asymptomatic hypoglycemias detected by the CGMS (glucose values <60 mg/dl) was analyzed in all of the monitored patients. This group included the 40 type 1 diabetic subjects in the CGMS group and all 30 type 2 diabetic patients. A summarized clinical description of all patients is provided in Table 1.

Statistical analysis was performed with SPSS/PC+ (version 10.0) statistics software. Descriptive data were expressed as the means ± SD (95% CI). The paired t test was used to compare HbA_{1c} levels before and after the study and to compare age and diabetes duration between groups. Fisher's test was used to compare sex distribution in the groups. $P < 0.05$ was considered to be statistically significant.

RESULTS — No statistical differences were found in age, sex distribution, or

HbA_{1c} before the study when comparing both groups of type 1 diabetic patients studied (Table 1).

The registers obtained for the group of type 1 diabetic patients monitored with the CGMS were analyzed, and therapy was modified as follows: in 31 case subjects, the type and doses of insulin were adapted to the glucose profile obtained; in 9 of the patients, treatment with continuous subcutaneous insulin infusion (CSII; Disetronic H-TRON plus V100, MiniMed 507C, or MiniMed 508) was started. Basal rate and boluses were calculated using the Disetronic or MiniMed algorithms (17,18) and adapted to the CGMS register.

In the group of type 1 diabetic control subjects, the glucose profile obtained after eight capillary measurements per day was used to modify treatment. The therapeutic modifications were as follows: in 25 patients, the type and doses of insulin were modified, and in 10 patients, treatment with CSII was started. Basal infusion and boluses were calculated on the same basis as the CGMS group and individually adapted to the glucose profile.

At 3 months after treatment modifications were made, HbA_{1c} levels were measured. A significant reduction was observed in both study groups. HbA_{1c} levels dropped from 8.3 ± 1.6 to 7.5 ± 1.2% ($P < 0.01$) in type 1 diabetic monitored patients and from 8.0 ± 1.4 to 7.5 ± 0.8% ($P < 0.01$) in the control group (Fig. 1). The subgroup of patients starting treatment with CSII showed the most improvement in terms of metabolic control. In those evaluated with the CGMS, the levels of HbA_{1c} dropped from 9.4 ± 2 to 7.2 ± 1.4% ($P < 0.01$), and in the control group, HbA_{1c} fell from 8.1 ±

Table 1—*Clinical characteristics of all patients included in the study*

	Type 1 diabetic subjects monitored with CGMS	Type 1 diabetic nonmonitored control subjects	Type 2 diabetic subjects monitored with CGMS
n	40	35	30
Sex (M/F)	18/22	17/18	17/13
Age (years)	36.5 ± 12	41 ± 10	58 ± 11
Diabetes duration (years)	17 ± 12	21 ± 10	12 ± 8
HbA_{1c} (%)	8.3 ± 1.6	8.0 ± 1.4	7.4 ± 1.6
Treatment	All with MII	All with MII	9 oral drugs, 20 MII, 1 CSII

Data are means ± SD, unless otherwise indicated. Oral drugs: metformin alone or in combination with sulphonylureas.
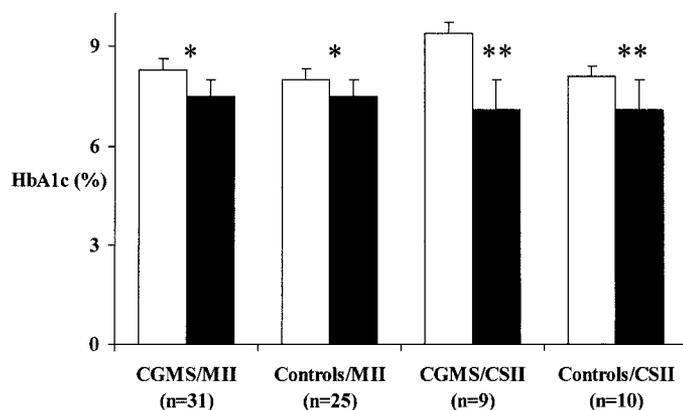
Figure 1—*The drop in HbA$_{1c}$ levels in type 1 diabetic patients 3 months after therapy modifications. A significant reduction in HbA$_{1c}$ was observed in all groups. The improvement in metabolic control was greater in those patients who started CSII therapy, regardless of the monitoring method. CGMS, patients monitored with the CGMS; CSII, patients who started insulin pump therapy; MII, patients treated with MIIs whose therapy was modified. *P < 0.05; **P < 0.01. □, Before; ■, after.*

1.8 to 7.1 ± 0.6% ($P < 0.01$). The subgroup of patients treated with MIIs also showed a significant reduction in HbA$_{1c}$ concentrations, from 8.0 ± 1.4 to 7.6 ± 1.1% ($P < 0.05$) for those previously evaluated with the CGMS, and from 8.0 ± 1.3 to 7.6 ± 0.9% ($P < 0.05$) for those in the control group (Fig. 1).

A total of 81 asymptomatic hypoglycemic events (glucose levels <60 mg/dl) lasting from 20 min to 7 h (mean duration 214 ± 288 min) were detected in 39 of the patients (55.7%) monitored with the CGMS. The frequency of these episodes was 62.5% in type 1 diabetic patients and 46.6% in type 2 diabetic patients. Moreover, the distribution of these events throughout the day was different depending on the type of diabetes. In 16% of the type 1 diabetic patients, hypoglycemia occurred during the day, whereas in 40% it happened at night; in the other 44% of patients, it occurred during both periods of time. The percentages of type 2 diabetic patients presenting asymptomatic hypoglycemias during the day and night were identical (42.8%), whereas they were detected in only 14.3% of the patients during both periods of time. The group of type 2 diabetic subjects with unrecognized hypoglycemias included five patients who were treated with hypoglycemic oral drugs (sulfonylureas in combination with metformin) (Fig. 2). No significant differences were detected in terms of sex, age, diabetes duration, diabetic complications, treatment, or HbA$_{1c}$ levels when patients with asymptomatic hypoglycemias were compared with those who recorded no hypoglycemias.

Patients felt confident and satisfied with CGMS use. Only five patients had problems understanding the instructions of the system. However, we observed some technical problems related to the use of the CGMS. First, nonoptimal coefficient correlations were obtained in the first patients studied on at least one of the monitoring-period days. This problem was partially solved by increasing the number of daily glucose values entered by the patient to at least five or six per day. We also observed technical problems at the beginning of the study related to the transition between days (at midnight); these problems were avoided by incorporating the new system software (version 1.7a). No skin lesions were observed (irritation, allergy, etc.), although eight subjects felt discomfort during the monitoring period. In six case subjects we had to replace the sensor immediately after insertion due to an "error" message. In 28 case subjects, the register was interrupted for several hours (from 15 min to 21 h, mean duration 422 ± 392 min) for no
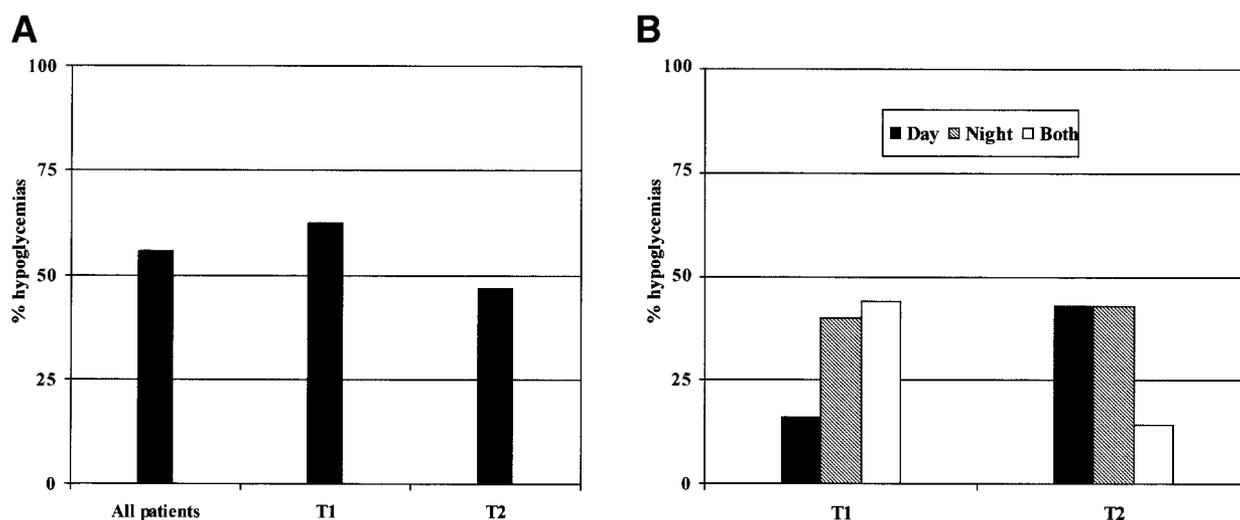

Figure 2—*A: Percentage of type 1 diabetic and type 2 diabetic patients with asymptomatic hypoglycemias detected by the CGMS. B: Daily distribution of asymptomatic hypoglycemias detected with the CGMS in type 1 diabetic (T1) and type 2 diabetic (T2) patients. Nocturnal asymptomatic hypoglycemic events were more frequent than diurnal ones. Type 1 diabetic subjects showed more episodes than type 2 diabetic subjects, especially at night or during both the day and night.*

Table 2—*Summary of the technical data obtained with the CGMS and the glucose meter during the monitoring period in 70 diabetic subjects*

	Number of readings	Glucose average (mg/dl)	Range of values		Correlation coefficient	Absolute difference	Number of paired readings
			Minimum	Maximum			
CGMS	816 ± 179	171 ± 80	52 ± 21	348 ± 74 }	0.82 ± 0.13 }	19 ± 7 }	16 ± 5 }
Glucose meter	19 ± 6	172 ± 45	74 ± 34*	295 ± 74*			

Data are means ± SD. *$P < 0.05$

apparent reason and without the alarm going off. In five cases, the alarm went off as a result of major discrepancies between sensor and glucose meter values.

Data on values obtained with the CGMS and the glucose meter are shown in Table 2. The mean recording duration was 68 ± 15 h. A good correlation coefficient was observed in 61 of the 70 case subjects. No significant differences were detected between the mean glucose values obtained using the CGMS and those obtained with the glucose meter, but the range of values measured was wider with the CGMS.

CONCLUSIONS — This study was designed to examine the real usefulness of the CGMS for deciding on treatment modifications in type 1 diabetic patients for whom glycemic control is difficult. We first started a protocol study in which type 1 diabetic patients were randomly assigned to either the CGMS group or the control group to evaluate the drop in HbA_{1c} concentrations 3 months after therapy modifications were made. Follow-up and medical care were the same for the control group and the study group. The metabolic control before the study was also similar. Our results apparently agree with previously published works that demonstrated the utility of the CGMS for modifying treatment and improving the metabolic control of diabetes (12,13, 15). However, our definitive data showed that the same improvement may be achieved using the information obtained from frequent fingersticks and more intensive patient follow-up than usual. In our study, both groups (CGMS and control) underwent the same improvement in metabolic control. In the subgroup of subjects monitored twice (before and after therapy modifications), the glucose profile in the second evaluation was better. This improvement in glucose patterns is associated with the drop in HbA_{1c} concentrations, but the frequent monitoring of capillary blood glucose levels of pa-

tients in the control group was enough to reduce HbA_{1c} levels to the same degree.

Although no published evidence has clearly demonstrated the superiority of CSII therapy compared with MII for improving metabolic control (19,20), our results demonstrated that the greatest reduction in HbA_{1c} concentrations was obtained in those patients using CSII therapy. In this subgroup of patients, prior use of the CGMS was not an additional advantage when determining the basal infusion rate of the pump. The same improvement in metabolic control was obtained in those patients whose basal infusion rate was calculated using theoretical algorithms.

Probably the most interesting finding of the study was the confirmation of the underestimated presence of unrecognized hypoglycemias in the diabetic population, especially during the nocturnal period. Despite a recent publication that described the sensor findings' as lower than anticipated in terms of its level of accuracy in showing spurious hypoglycemias (21), other studies have demonstrated good response and accuracy of CGMS measurements during hypoglycemia (22), and some other studies have detected a high frequency of clinically nondetected hypoglycemias in type 1 diabetic patients (15,16,23,24). Our study demonstrated a high incidence of this event in type 2 diabetic patients. Type 1 diabetic subjects had more episodes, especially at night. However, the number of type 2 diabetic patients with nocturnal hypoglycemias was also high, and some of these patients were not on insulin treatment but were taking short-acting sulfonylureas (glimepiride, glipizide, and gliclazide). The reported incidence of sulfonylurea-induced hypoglycemia (basically caused by longer-acting preparations, such as chlorpropamide and glibenclamide) is 19 cases per 1,000 patients per year (25), but according to our findings, the real incidence could be higher.

In a population such as patients with type 2 diabetes, who have a high risk of suffering from heart disease and stroke, avoiding hypoglycemic events is especially important. When the stress of acute hypoglycemia is inflicted upon a diseased vascular system, ischemic events can be precipitated by the hemodynamic and hemostatic changes associated with hypoglycemia (25). A recently published article on hypoglycemia and diabetes describes the presence of nondetected hypoglycemias in type 2 diabetic subjects, but only in those with a very long diabetes duration and final insulin deficiency (26). In our study group of type 2 diabetic subjects, the diabetes duration was not very long, and no final insulin deficiencies were found. For a long time, the presence of autonomic neuropathy was one of the explanations for the absence of easily recognizable sympathetic symptoms produced by hypoglycemia. More recent works have demonstrated that iatrogenic hypoglycemia causes both defective glucose counterregulation (reducing the epinephrine response in the presence of an absent glucagon response) and hypoglycemia unawareness (by reducing sympathetic neural and adrenal response) (27). Accordingly, in our study, the preliminary results of a subgroup of patients whose autonomic neuropathy was analyzed showed no significant differences in the prevalence of autonomic neuropathy between subjects with and without asymptomatic hypoglycemic events (unpublished data). It will not be possible to reach a definitive conclusion until all of the patients in the study have been evaluated for autonomic neuropathy. We found no significant differences at the beginning of the study in terms of sex, age, diabetes duration, HbA_{1c} concentrations, or the presence of retinopathy and nephropathy when patients with and without unrecognized hypoglycemias were compared.

Extensive information is not available on the technical problems and complica-

tions related to the CGMS (21,28,29), but in our experience it is common for technical problems to arise, especially in the beginning of CGMS use. These problems can partly be solved through adequate training of medical staff and patients and through accumulative experience. One of the initial problems found was that the CGMS instructions for use recommend entering four capillary glucose measurements per day in order to calibrate the system. In our experience, the number of measurements performed per day should be increased to at least five and, ideally, six in order to obtain an optimal correlation coefficient.

In summary, in this study the CGMS was not more useful for improving metabolic control than frequent measurement of capillary blood glucose levels, but it demonstrated a very high incidence of nocturnal asymptomatic hypoglycemias in type 2 diabetic subjects treated with oral agents.

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