The Glucose Area Under the Profiles Obtained With Continuous Glucose Monitoring System Relationships With HbA_{1c} in Pediatric Type 1 Diabetic Patients

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OBJECTIVE — The purpose of this study was to determine whether the continuous glucose monitoring system (CGMS) (MiniMed, Sylmar, CA) *1*) is sufficiently representative of the overall metabolic control as assessed by HbA_{1c}, *2*) could be used to identify a particular blood glucose threshold value affecting hemoglobin glycation; and *3*) is able to show any relationship between particular glycemic profiles and HbA_{1c} levels.

RESEARCH DESIGN AND METHODS — Of 44 pediatric patients with type 1 diabetes who wore CGMS devices, 28 subjects were selected for the study. Criteria for inclusion were high levels of HbA_{1c} (≥8%) for more than 1 year or a history of frequent hypoglycemic episodes and a complete CGMS registration for 72 h. Age of the subjects ranged from 5.7 to 24.8 years, the mean duration of disease was 7.63 ± 4.75 years, and the mean HbA_{1c} value was 8.7 ± 1.3%. CGMS data were downloaded and glucose profiles were analyzed. The area under each glucose profile was calculated by means of a professional digital planimeter.

RESULTS — The glucose profiles showed a high frequency of prolonged hyperglycemic periods (80% of subjects) and a low frequency of postmeal glycemic peaks (29% of subjects). Postlunch values were significantly correlated with HbA_{1c} levels, but the correlation disappeared when controlling for glucose area values. Glucose area values significantly correlated with HbA_{1c} levels both when considered as a whole (40–400 mg/dl; $r = 0.53$, $P = 0.002$) and when considered fractioned (40–150, 40–200, 40–250, 40–300 mg/dl), apart from the 40–90 mg/dl partial area. HbA_{1c} levels were significantly decreased 3 and 6 months after use of CGMS ($P = 0.05$ and 0.03, respectively, paired Student's *t* test) .

CONCLUSIONS — HbA_{1c} levels may be decreased by using the information obtained with the CGMS. Three-day glucose profiles are representative of the overall glucose control, because glucose area values correlate with HbA_{1c} levels. The only glucose threshold below which there seems to be no correlation with HbA_{1c} is 90 mg/dl. Only glucose area, and not postprandial glucose values, are directly and independently correlated with HbA_{1c}. Therefore, to improve metabolic control, it is necessary to lower the whole mean 24-h glycemia and not just the postprandial glucose values.

Diabetes Care **25:1840–1844, 2002**

The recent availability of a home continuous glucose monitoring system (CGMS) represents an important advance in the management of subjects with type 1 diabetes (1–3). In fact, the minute-by-minute recording of the glucose levels in outpatient subjects has presented a unique opportunity to identify unknown glucose excursions in an attempt to optimize insulin therapy and also to investigate areas of controversy in clinical diabetes research. So far, few studies on diabetic children have been published (4–6). One of these studies (4) reported a short-term improvement in HbA_{1c} levels in a small number of subjects after the use of the CGMS device and the subsequent adjustment of insulin doses or meal schedules. A second study (5) described several recordings of asymptomatic hypoglycemic periods and a high frequency of unexpected postprandial peaks despite target glucose preprandial levels and satisfactory HbA_{1c} values. A third and very recent study on a larger series of patients confirmed the positive impact of CGMS on glycemic outcome (6).

Our study of CGMSs (Minimed, Sylmar, CA) in children and adolescents with diabetes began in September 2000. The aim of this study was to determine *1*) whether a 3-day glucose profile is sufficiently representative of the whole metabolic control of a patient; *2*) whether it is possible to reduce HbA_{1c} levels in the short term through the modifications suggested by CGMS; *3*) whether it is possible to identify a particular blood glucose mean value, which may contribute more to the glycation of hemoglobin; and *4*) whether it is possible to identify particular glucose profiles in subjects with better or worse metabolic control.

RESEARCH DESIGN AND METHODS

Patients

Beginning in September 2000, 44 diabetic outpatient children and adolescent subjects, who were among the >300 diabetic patients followed regularly at our clinic, wore a CGMS device. Informed consent was obtained from participants

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Received for publication 8 February 2002 and accepted in revised form 24 June 2002.
Abbreviations: CGMS, continuous glucose monitoring system.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(and their parents if the patient was aged <18 years). Among the patients tested, 28 subjects were selected for the study. Criteria for inclusion were high levels of HbA_{1c} (≥8%) for more than 1 year or a history of frequent hypoglycemic episodes and a complete registration without interruption in the sensor tracing for 72 h. Ages ranged between 5.7 and 24.8 years (mean 14.8 ± 4.8 years) and duration of disease ranged from 2 to 19.4 years (mean 7.63 ± 4.74 years). In all patients, HbA_{1c} and fructosamine levels were evaluated within 2 weeks before the sensor application and mean values were 8.7 ± 1.3% (range 6.6–11.9%; ≥8% in 19 patients and <8% in 9 patients) and 412.8 ± 59.5 μmol/l (range 330–557 μmol/l), respectively. HbA_{1c} and fructosamine levels were reevaluated 3 months (in 24 patients) and 6 months (22 patients) after wearing the CGMS device and after appropriate changes of diet or insulin regimens suggested by CGMS. A total of 26 patients received three insulin injections per day; NPH insulin was combined with short-acting insulin (regular insulin in 18 patients and insulin lispro in 8 patients) before breakfast and dinner and short-acting insulin alone was given before lunch (regular insulin in 18 patients and insulin lispro in 8 patients). Two patients received four insulin injections per day; insulin lispro was given before meals and NPH insulin was given at bedtime. None of the patients was on continuous subcutaneous insulin infusion.

Study methods

The CGMS system is approved for use as a Holter-type monitor; its characteristics have been described repeatedly elsewhere (1,2). In brief, all patients and families were instructed in the use of the CGMS device and were asked to enter at least four daily self-monitoring capillary blood glucose measurements obtained with a personal glucometer into the instrument for calibration. They were also asked to keep detailed written records of any particular event (insulin dose, food intake, etc.) and to code these events into the monitor. For four patients, the event recordings were missing. The patients were also told to modify their usual daily behavior as little as possible during the test. The system was well tolerated by all patients. After 3 days, the data were downloaded via the Com-Station using the MiniMed Solutions Software version 2.0b (MiniMed, Sylmar, CA), and the 24-h glucose profile obtained for each of the 3 days was analyzed. In particular, we counted the number of glucose periods ≤40 mg/dl and ≥400 mg/dl, the number of rapid glycemic excursions (peaks with increase and subsequent decrease of glucose values ≥200 mg/dl in 3–4 h), the number of prolonged periods of hyperglycemia (blood glucose values >250 mg/dl for >5 h), and all preprandial and postprandial glucose levels (1 and 2 h after each main meal, i.e., breakfast, lunch, and dinner).

Furthermore, we calculated the whole area under the curve of each 24-h glucose profile within the range of the CGMS (40–400 mg/dl). For each subject, we evaluated both the mean value of the areas of the 3 days and the sum of the areas of the same 3 days. All these areas were measured twice by the same operator (R.S.) using a professional digital planimeter (Koizumi Plakom KP-80N) and expressed in centimeters squared. We considered the mean value of two measurements (mean difference between the two readings <1%). Finally, we calculated also some partial areas of artificial glucose profiles, i.e., those obtained by cutting horizontally the whole profile (40–400 mg/dl) to an arbitrary upper cutoff, established at 90, 150, 200, 250, and 300 mg/dl.

HbA_{1c} was measured by high-performance liquid chromatography (Auto A_{1c} TM Analyzer HA 8140; Kyoto Daiichi, Kagaku, Japan) (normal range 3.8–5.8%), and fructosamine was measured by colorimetric method (NBT; Roche, Montclair, NJ) (normal range 200–285 μmol/l).

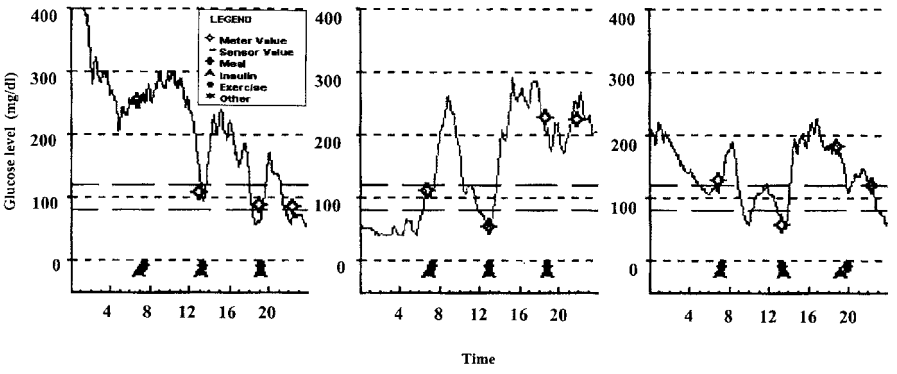

Figure 1—*The glucose sensor profile from an 11-year-old diabetic patient with frequent hypoglycemic episodes and high day-to-day variability of glucose profiles.*

Statistical analysis

The variables presented were summarized as means ± SD. The data collected were processed with Student's *t* test, paired Student's *t* test, and *r* Pearson correlation coefficient. Multiple linear regression analysis was used to evaluate the influence of postprandial glucose levels and glucose area on HbA_{1c} levels. The computer software Statistical Package for Social Science (SPSS, Chicago, IL) was used on an IBM computer. All results nominally significant at $P < 0.05$ were indicated.

RESULTS

Glucose areas

The mean 3-day whole glucose area value was 98.6 ± 27.1 cm^2 (range 38.1–157.6 cm^2) and the mean value of the sum of the 3-day glucose areas was 298.0 ± 85.4 cm^2 (range 114.3–472.9 cm^2). The day-by-day intrapatient variability of the glucose area values was >50% in 14 of 28 patients (50%) and ≥100% in 7 of 28 patients (25%), even in the absence of consistent changes of the insulin dose (Fig. 1).

Mean 3-day glucose area values correlated positively with HbA_{1c} and fructosamine levels (Table 1). HbA_{1c} and fructosamine values correlated positively also with the partial glucose area values 40–150, 40–200, 40–250, and 40–300 mg/dl, whereas they did not correlate with the partial area 40–90 mg/dl (Table 1). The same results were obtained by considering the sum of the 3-day glucose area values.

Table 1—*Correlation between HbA_{1c} or fructosamine and mean 3-day glucose area values, calculated both under the whole glucose profile 40 and 400 mg/dl and under the partial glucose profiles*

Mean 3-day glucose area values	HbA_{1c}		Fructosamine	
	r	*P*	*r*	*P*
40–90 mg/dl	0.27	NS	0.30	NS
40–150 mg/dl	0.47	0.007	0.56	0.001
40–200 mg/dl	0.49	0.004	0.57	0.001
40–250 mg/dl	0.55	0.001	0.61	0.0001
40–300 mg/dl	0.54	0.002	0.60	0.0001
40–400 mg/dl	0.53	0.002	0.64	0.0001

NS, not significant.

Metabolic control

HbA_{1c} levels 3 and 6 months after wearing of the CGMS device were significantly lower than baseline values (paired Student's *t* test, $P = 0.05$ and 0.032, respectively), and the reduction in HbA_{1c} was $-0.40 \pm 0.94\%$ at 3 months and $-0.43 \pm 0.87\%$ at 6 months. A decrease of ≥1% was maintained for 6 months in five patients.

Glucose profiles

Asymptomatic nocturnal hypoglycemic episodes with glucose values ≤40 mg/dl were recorded in almost 50% of the patients (12 of 28), consistent with 18% of the nights (15 of 84). Prolonged hyperglycemic periods (Fig. 2*A*) were found in >80% of the patients (23 of 28) and values ≥400 mg/dl were found in 15 of 28 patients (54%), 5 of whom had HbA_{1c} values <8%. Rapid glycemic excursions (Fig. 2*B*) were recorded in 8 of 28 patients (29%), more frequently after hypoglycemic episodes (6 patients) than after meals (2 patients). The patients showing peaks did not differ from those in whom peaks were not noted, both regarding glucose area values and for HbA_{1c} levels. The rare presence of postprandial peaks was confirmed by finding glucose level means 1 or 2 h after main meals similar to or lower than mean preprandial values. The latter were always >150 mg/dl (Fig. 3). By subdividing the patients according to HbA_{1c} levels >8% and <8%, we found significantly higher premeal glucose levels and glucose area values in the group with HbA_{1c} ≥8%, whereas the postprandial peaks were similar in the two groups (Fig. 4). Premeal and postmeal glucose levels correlated with the glucose area values.

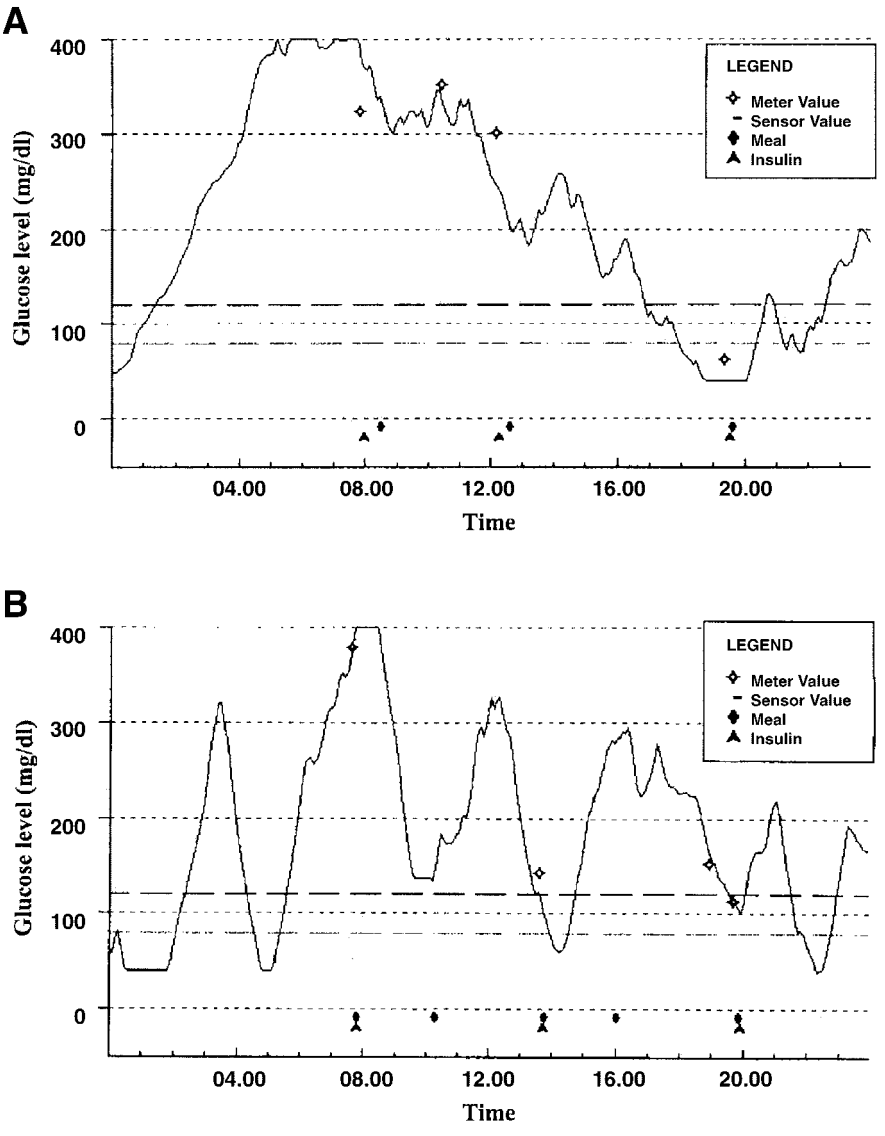

Figure 2—*An example of a prolonged hyperglycemic period in a 15-year-old girl with HbA_{1c} = 9.1% (A) and rapid glycemic excursions in a 12.5-year-old boy with HbA_{1c} = 7.5% (B).*

The level of significance was higher for postlunch ($r = 0.65$, $P < 0.0001$) and prelunch ($r = 0.58$, $P = 0.003$) values and lower for prebreakfast ($r = 0.43$, $P = 0.04$) and postbreakfast ($r = 0.39$, $P = 0.06$, not significant) values. HbA_{1c} values correlated significantly only with postlunch glucose levels ($r = 0.45$, $P = 0.029$) and not with the other pre- and postmeal glucose levels. However, using multiple regression analysis, the correlation with postlunch glucose levels disappeared, and HbA_{1c} levels were significantly influenced only by glucose area values ($R^2 = 0.49$, $P = 0.0002$).

CONCLUSIONS— The use of CGMS has opened a new window through which it is possible to observe directly in vivo what happens to patients with diabetes. This new device shows both predictable and known situations and unpredictable events. The first striking observation in our pediatric population is the marked intrapatient day-by-day variability of the glycemic profile, even in the absence of significant changes in the usual daily schedule (type and dose of insulin, diet, and physical activity). Despite this variability, our findings seem to demonstrate that the data obtained with CGMS in only 3 days are not casual but represent a reliable indicator of the overall metabolic control of that patient. In fact, the whole glucose amount of the 3 days, expressed as area under the curve, signif-

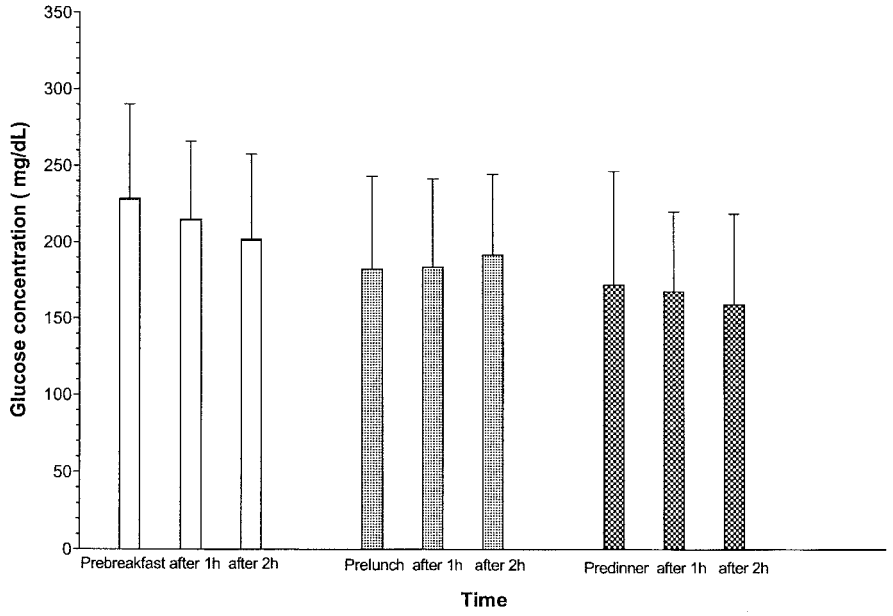

Figure 3—*Pre- and postmeal glucose values (mean ± SD) in the 24 diabetic patients wearing the CGMS device for 3 days and coding the event-meal into the monitor.*

icantly correlated with fructosamine and HbA_{1c} levels. The degree of this correlation, furthermore, is similar to that reported in a recent study (7) between HbA_{1c} levels and the mean of three or more daily home blood glucose measurements over 30 days in a large group of pediatric and young diabetic patients. Therefore, the information provided by the CGMS device during 3 days seem to be of the same importance as multidaily capillary blood glucose tests performed in a period of time 10 times longer. This would mean that also in poorly compliant patients, such as adolescents, who do not always perform self-monitoring of blood glucose, it is possible to obtain information useful to modifying the insulin treatment and decreasing HbA_{1c} levels. This occurred in some of our poorly compliant patients, in whom the improvement in HbA_{1c} levels was sustained for 6 months. If we consider that these subjects showed persistently poor or progressively worsening metabolic control for >1 year, it can be hypothesized that this improvement was not merely a study effect but was due to the modifications of therapy and behavior based on CGMS results. On the other hand, our findings are in agreement with those reported both in a trial including few pediatric patients (4) and, more recently, in a larger group of children and adolescents with poor metabolic control (6). Although the accuracy of sensor glucose measurements during hypoglycemia has not yet been validated, we found, in agreement with other reports (4–6), a high frequency of asymptomatic nocturnal hypoglycemic episodes. Furthermore, as in the study by Kaufman et al. (6), we found little evidence of postprandial peaks, but we often recorded peaks after hypoglycemic episodes with a tendency to recur in the same day, as shown in Fig. 2*B*. A similar pattern of marked glycemic fluctuations was reported by Kovatchev et al. (8) as a characteristic preceding and following severe hypoglycemic episodes. Different from this study, our blood glucose disturbances escorted only mild hypoglycemic episodes, probably because our patients were younger and presumably had a more efficient counter-regulatory system. In our patients, glucose area and premeal glucose values, but not postmeal values, were higher in the subjects with poor control than in those with satisfactory control. Different results were obtained in a group of pediatric patients by Boland et al. (5), who revealed by means of the CGMS surprisingly profound postprandial hyperglycemia despite excellent HbA_{1c} levels. It is likely that our patients, who differed from the latter in not using insulin pumps and in worse HbA_{1c} values, did not show brief hyperglycemic episodes, such as postprandial, because they showed high glucose levels throughout most of the day. At the present time, it is controversial whether fasting or postprandial glycemia has more impact on diabetic control (9). According to our data,

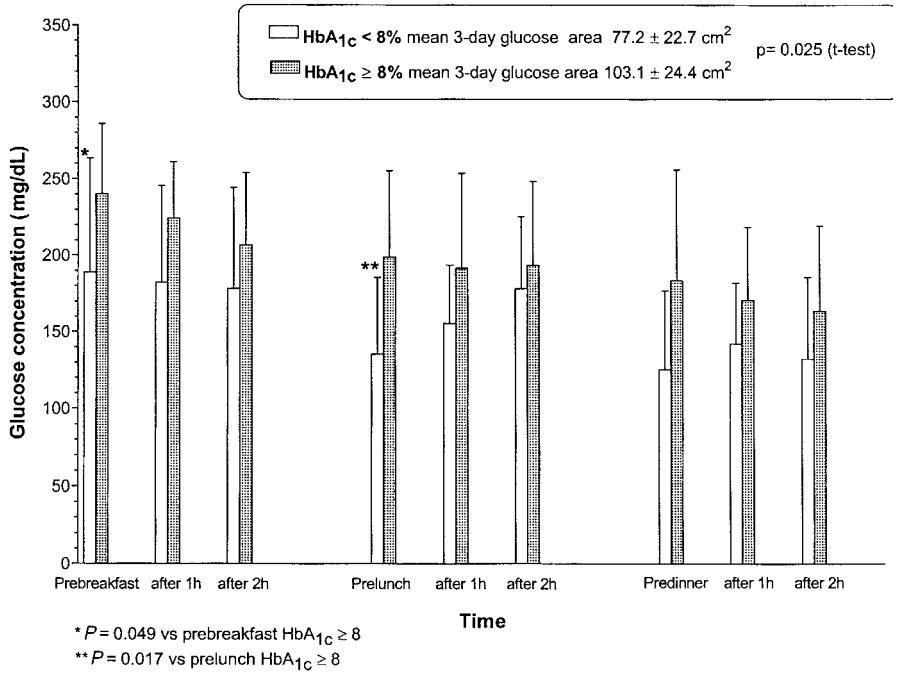

Figure 4—*Pre- and postmeal glucose values (mean ± SD) in the 24 diabetic CGMS participants coding the event-meal into the monitor subdivided according to good or bad metabolic control (HbA_{1c} levels <8% or ≥8%).*

it seems that the whole daily glycemia, and not a single glucose value, is an important determinant in the overall glycemic control, as measured by HbA_{1c}. In fact, using multiple regression analysis, whereas the significant correlation between glucose area and HbA_{1c} was confirmed, the correlation between postlunch glucose value and HbA_{1c} level disappeared when controlling for the glycemic area value. Therefore, postprandial glucose level, the subject of many recent studies (10–13), probably plays an effectively important role in the overall glucose control, not in itself, but rather as an expression of the whole daily blood glucose concentration. In fact, postprandial glucose level, particularly postlunch, was strictly correlated with glucose area value in our patients. Our results indicate that the efforts to improve HbA_{1c} should be directed toward lowering not only postprandial values but, above all, the whole 24-h glycemic profile. This can be obtained by modifyng insulin schedule, food intake, and lifestyle patient by patient.

The importance of the overall glucose area is further supported by its influence on hemoglobin glycation, even when it is only moderately above the normal range. All the amounts of glucose >90 mg/dl, in fact, including those within 150 mg/dl, were correlated with fructosamine and HbA_{1c} levels. Therefore, these findings seem to demonstrate that there is not a glucose threshold level in influencing HbA_{1c}.

We can conclude that *1*) CGMS is of clinical utility in routine clinical practice, because the 3-day glucose profile is representative of the overall control of the patient, similar to a 1-month self-control of blood glucose; *2*) it is possible to improve metabolic control and decrease HbA_{1c} by following the modifications suggested by the CGMS; *3*) the only glucose threshold below which there is no correlation with HbA_{1c} is 90 mg/dl; and *4*) it seems that postprandial peaks have an impact on the overall metabolic outcome not in themselves, but rather as an expression of the whole daily glucose area. This is the only parameter directly and independently related to HbA_{1c}.

Further studies of glucose area obtained with the CGMS in larger series of patients will provide support for these findings and will be useful in solving this and other controversies in clinical diabetes research.

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