Frequency of Early-Morning Rise in Blood Glucose in Children With Diabetes at Camp

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To estimate the frequency of an early-morning glucose rise (EMR) in relatively unselected children with insulin-dependent diabetes mellitus (IDDM), we assessed capillary blood glucose (CBG) at midsleep (0200–0430) and prebreakfast (0700–0800) in 97 children with diabetes at camp. The EMR (prebreakfast CBG–midsleep CGB) was inversely related to the midsleep CBG level ($r = -.45$, $P < .001$). Of the 49 children with midsleep CBG <200 mg/dl, the mean EMR was 34 ± 60 mg/dl, and 18 of these children had rises of >40 mg/dl. In conclusion, when midsleep glycemia is <200 mg/dl, a rise in blood glucose from midsleep to prebreakfast, often >40 mg/dl, is a common element of glycemic control among children with IDDM. The relative importance of the Somogyi phenomenon, the dawn phenomenon, and mere insulin insufficiency in the early-morning hours cannot be determined from these data. *Diabetes Care* 11:574–78, 1988

Until recently, there have been relatively few data on which to base discussions of overnight blood glucose patterns in insulin-dependent diabetes mellitus (IDDM) (1). The general belief that fasting morning hyperglycemia was either just a part of general poor control or the result of rebound hyperglycemia (the Somogyi phenomenon; 2) has recently given way to a broader understanding in which the dawn phenomenon, e.g., a tendency for blood glucose to rise in the early-morning hours in the absence of nocturnal hypoglycemia, has been increasingly recognized as an important component (3–9).

Although this rethinking of nocturnal glycemic control has generated new lines of investigation, the frequency of an early-morning rise (EMR), be it due to the dawn or Somogyi phenomenon or both, remains basically unknown. To date, the few estimates of the frequency of these phenomena have tended to be in clinic-based groups of patients generally seen at tertiary-care facilities (10–13). As such, these estimates are of limited generalizability to people with IDDM in the general population.

This study was undertaken to describe the pattern of overnight control and of early-morning changes in blood glucose in a relatively unselected population of children with diabetes at camp. Specifically, our purpose was to describe *1*) the frequency of the glucose EMR, *2*) the consistency of the rise during 2 consecutive days, and *3*) the influence of overnight control on this frequency and consistency.

MATERIALS AND METHODS

Ninety-seven children were studied while they attended Eagle's Nest Camp for Children with Diabetes, Brevard, North Carolina. Informed consent was obtained from all participants in accord with the standards of the Committee on Protection of the Rights of Human Subjects of the University of North Carolina School of Medicine. Approximately 10% of the campers did not participate in the study, generally due to previously scheduled camp activities that prohibited nocturnal glucose collection during the study day. As assessed by question-

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naire, the children studied had a mean age of 12.1 yr (range 7–18 yr) and a mean duration of diabetes of 4.4 yr (range 1–11 yr). None had clinically important renal or retinal disease. All were insulin treated, the majority receiving split-mixed insulin regimens with evening injections administered in a supervised setting at ~1700, immediately preceding the evening meal. The study was initiated after 7 days of camp. Before the study day, camp physicians routinely adjusted insulin schedules in an attempt to adjust for camp activities and to maximize control. Data gained from four daily glucose measurements, which in most children were capillary blood glucose (CBG), guided these efforts. Food ingestion was monitored within a program of health education. In this isolated camp setting, food was available only at main meals and scheduled snacks. At each main meal the children were instructed on how to use a food-exchange plan to select an adequate diet among the foods offered that day. The use of this plan was supervised by camp physicians, cabin clinicians, and trained camp staff who sat with the children at meal tables. An evening snack was given before bedtime, and each child received his/her snack in a closely supervised setting.

For purposes of this study, CBG was measured by 10 cabin clinicians—physicians, medical students, or allied-health professionals specifically trained in and responsible for glucose monitoring of the children. Measurements were obtained with Glucoscan 1 (Lifescan, Mountain View, CA) machines, specially calibrated and specifically adapted for Glucoscan strips. These machines were calibrated against quality-control standards immediately before initiating the study. For each child, the same observer and machine measured midsleep and prebreakfast CBG. Midsleep CBG collection was performed during routine nocturnal rounds checking for hypoglycemia. Children were informed before they retired that they would receive a finger puncture for CBG determination during these rounds. Although some of the children momentarily awoke during the collection, the majority remained asleep. Midsleep CBG was obtained between 0200 and 0430 and prebreakfast CBG between 0700 and 0800. The EMR is defined as prebreakfast minus midsleep CBG.

Nocturnal hypoglycemia was defined as CBG <60 mg/dl obtained either at the midsleep measurement or, if symptomatic, at some other time during the usual sleeping hours of the child. Children with CBG levels indicative of nocturnal hypoglycemia received 10–12 g carbohydrate, generally delivered as 8 oz milk.

Adjustment for statistical regression to the mean due to intraobserver midsleep CBG measurement error was performed with parametric empirical Bayes inference (14,15). This adjustment is performed to characterize the degree to which random variation resulting from interobserver midsleep CBG-measurement error contributed to the glucose EMR. With a logarithmic transformation to account for variance heteroscedascity in measurement error (i.e., variance of differing magnitude along the spectrum of measurement error), the statistic $\hat{\rho}$ was calculated as $\hat{\rho} = \tau^2/s^2$, where τ^2 is intraobserver variance obtained from a series of repeated measurement of blinded, standard solutions by the cabin clinicians and s^2 is total sample variance. This statistic is an estimate of the relative contribution of intraobserver to total variation. Next, an empirical Bayes estimate of midsleep CBG was determined for each child, with the formula $\tilde{X}_i = \hat{\rho}\bar{X} + (1 - \hat{\rho})X_i$, where $\tilde{X}_i$ is the empirical Bayes estimate for a midsleep CBG, $\bar{X}$ is the mean midsleep CBG, and X_i is the observed midsleep CBG. An adjusted EMR, for which that part of the EMR due to this statistical regression to the mean has been removed, was then calculated by use of the adjusted midsleep CBG. Data, unless otherwise stated, are presented unadjusted. Correlations are expressed with Pearson's product-moment correlation coefficient (r).

RESULTS

Overall mean midsleep and prebreakfast CBG for the 97 children were 198.6 ± 91.7 and 198.8 ± 87.4 mg/dl, respectively, with a resultant trivial (0.2 mg/dl) mean EMR. Nearly equal numbers of children had early-morning rises and falls.

Figure 1 illustrates a strong linear relationship between the EMR and midsleep CBG. As can be seen, for children with midsleep CBG less than the mean (~200 mg/dl), blood glucose tended to rise in the early morning, whereas for those with midsleep CBG >200 mg/dl, blood glucose tended to fall. A best-fit least-squares regression of the relationship (Fig. 1, *solid*

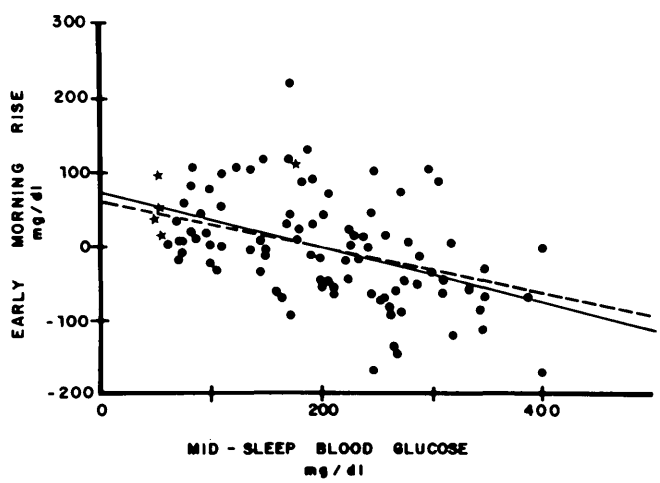

FIG. 1. Scattergram of relationship between midsleep capillary blood glucose (CBG) and early-morning rise (EMR) in blood glucose in 97 children with diabetes at camp. Least-squares best-fit regression line (EMR = 69 − .35 midsleep CBG; r = .45, P < .001) for crude values is shown by *solid line* and similar relationship for adjusted values (EMR = 62 − .30 midsleep CBG; r = −.38, P < .001) is shown by *dashed line*. ⋆, Children with documented nocturnal hypoglycemia.

TABLE 1
Effect of midsleep capillary blood glucose on magnitude and frequency of early-morning rise in blood glucose in 97 children with diabetes at camp

Midsleep CBG (mg/dl)	*n*	Crude magnitude of EMR	Adjusted magnitude of EMR	Frequency of crude EMRs of various magnitudes (mg/dl)					
				≤0		1–39		≥40	
				n	%*	*n*	%*	*n*	%*
>200	48	−34.2 ± 65.3	−26.8 ± 64.4	34	71	7	15	7	15
121–200	24	37.7 ± 74.8	37.3 ± 74.9	9	38	5	20	10	42
81–120	14	34.4 ± 42.7	31.0 ± 42.6	3	21	5	36	6	43
≤80	11	25.4 ± 31.4	21.6 ± 31.5	2	18	6	54	3	27
Total	97	0.23 ± 71.0	2.89 ± 68.6	48	49	23	24	26	27

Values are means ± SD. EMR, early-morning rise; CBG, capillary blood glucose.
*Percentage of row total.

line: EMR = 69 − 0.35 midsleep CBG; $r = -.45$, $P < .001$) demonstrates a 1 mg/dl addition to the EMR for every 0.35 mg/dl diminution in the level of midsleep CBG. Recalculation of this relationship, after removing the five children with documented hypoglycemia, resulted in little change (EMR = 64 − 0.33 midsleep CBG; $r = -.41$, $P < .001$).

Table 1, in which the magnitude of the EMR is presented for various levels of midsleep CBG, confirms this dependency of the EMR on the midsleep CBG value. Most of those with midsleep CBG >200 mg/dl had either falls or trivial rises in CBG in the early morning. For those with midsleep CBG <200 mg/dl, the situation is quite different. A large EMR was seen in each of the three lowest subgroups of midsleep CBG: ≤80 mg/dl, between 81 and 120 mg/dl, and between 121 and 200 mg/dl. As CBG at midsleep decreased, an increasing proportion of children had an EMR, and overall, 39% had rises of >40 mg/dl.

Adjustment of the data to account for regression to the mean secondary to intraobserver variability in CBG measurement produced little change in these results.

TABLE 2
Stability of major early-morning rises

Midsleep CBG on day 1 (mg/dl)	*n*	Early-morning rise on day 2 (*n*)		
		≤0 mg/dl	1–39 mg/dl	≥40 mg/dl
>200	8	4	1	3
≤200	17*	3	4	10
Total	25	7	5	13

Frequency and magnitude of rises on day 2 for children with diabetes at camp with rises >40 mg/dl on day 1, examined separately for those with midsleep capillary blood glucose greater and less than 200 mg/dl. CBG, capillary blood glucose.
*Of 18 children with midsleep CBG <200 mg/dl and an early-morning rise >40 mg/dl on day 1, 1 was not measured on day 2.

The adjusted linear relationship (Fig. 1, *dashed line*: EMR = 62 − 0.30 midsleep CBG; $r = -.38$, $P < .001$) differed only slightly from the unadjusted one. The magnitude of the adjusted EMR was only minimally affected (Table 1). The adjusted rises, as would be expected, tended to be smaller. Yet, among camping children with midsleep CBG <200 mg/dl, the frequency of rises of >40 mg/dl (19 children with unadjusted data, 18 children with adjusted data) was virtually unchanged.

To examine the stability of major EMRs, the consistency of the EMR in children with rises >40 mg/dl ($n = 25$) was examined (Table 2). For the 8 individuals with midsleep CBG >200 mg/dl on the 1st day, no consistency was found; 4 had decreasing and 4 had increasing glycemia during the second early-morning period. However, for the 17 campers with midsleep CBG <200 mg/dl on the 1st day and values measured on the following day, 14 had rises, 10 of which were also >40 mg/dl.

Of the five documented nocturnal hypoglycemias, four were identified during the study's midsleep measurement and one by an earlier nocturnal measurement performed in response to symptoms. These five children had a mean EMR of 63 ± 43.1 mg/dl; three had an EMR >40 mg/dl.

To evaluate the effect of nocturnal hypoglycemia on prebreakfast CBG, the frequency of nocturnal hypoglycemia at different levels of prebreakfast CBG was examined next. Three of 29 children with low to normal prebreakfast CBG (54–140 mg/dl) had documented hypoglycemia, with midsleep values of ≤60 mg/dl. Among the 68 children with prebreakfast hyperglycemia (≥140 mg/dl), the majority (62 children) had midsleep values of ≥120 mg/dl—quite removed, at least at that time, from a risk of hypoglycemia. One of the 62 had symptomatic hypoglycemia earlier in the night. Five of the 68 had midsleep values between 80 and 120 mg/dl, and only 1 had documented midsleep hypoglycemia, with a value of 51 mg/dl.

DISCUSSION

The state of early-morning glycemia is remarkably dynamic—remarkable for its variability at a time when, in general, the metabolic system is assumed to be nearly in resting condition. Averaging values of different individuals masks the importance of these changes by hiding their heterogeneity, because the tendency for glycemia to fall in children with midsleep CBG >200 mg/dl is balanced by the tendency of glycemia to rise in those with midsleep CBG <200 mg/dl. Patients selected because they represent an extreme value in a distribution can be expected, on the average, to have less extreme values on subsequent measurements. This is called regression to the mean (16). Overall, the pattern observed here is one of regression to the mean; those with relatively high values at measurement one (midsleep) have fallen toward the mean by measurement two (prebreakfast), whereas those with relatively low values have risen.

Such regression can stem from two sources: one biologic, i.e., arising by virtue of physiologic mechanisms (many homeostatic), and the other one statistical, i.e., a systematic artifact stemming principally from random measurement error at the first reading. As a result of that reading, the children were classified as belonging to one extreme (CBG <200 mg/dl) or the other (CBG >200 mg/dl). [Because children were not categorized by prebreakfast CBG, no adjustment for random measurement error in prebreakfast CBG was necessary.] The fact that the adjusted analysis, which controlled for intraobserver variability in reading, the source of such random variability, produced but a trivial change in the relationship found, argues that the bulk of the regression reported is biologic in origin. That this pattern noted in early-morning glycemia is one of biologic regression to the mean negates neither its validity nor its importance.

Homeostatic mechanisms account for part of this biologic regression. For example, in hyperglycemic states, renal glucose clearance and suppression of hepatic glucose production work to bring glycemia back toward normal (17). At the other end of the spectrum, insulin resistance after hypoglycemia, the Somogyi phenomenon (2), may lead to a glucose rise.

What are notable in these data are not the frequent falls in glycemia among hyperglycemic children, as they are more readily explanable, but rather the EMRs that occurred in most campers with midsleep glycemia <200 mg/dl. The 49 children with CBG <200 mg/dl had a mean EMR of 34 mg/dl, more than one-third of these children had EMRs >40 mg/dl, and for most of these children, the rise was consistent in direction and magnitude over the 2 measurement days.

The Somogyi phenomenon can, at best, account for only a fraction of these rises, as the frequency of documented hypoglycemia in the children studied was small in relation to the frequency of substantial EMRs. Furthermore, despite nocturnal hypoglycemia treatment, three of the five children with nocturnal hypoglycemia had prebreakfast CBG <140 mg/dl, certainly not the rise expected from the classic Somogyi phenomenon as described in the literature.

The relative contributions of insulin insufficiency and the dawn phenomenon, i.e., the early-morning ascending phase of a circadian glucose rhythm, cannot be determined from these data. It seems logical that these two factors would act together.

Thus, for a given value of midsleep glycemia, the combination of these four factors—the dawn phenomenon, the availability of insulin, homeostatic mechanisms tending to lower glycemia, and homeostatic mechanisms tending to raise glycemia—the action of the latter two related to the level of glycemia at midsleep, will determine the likelihood of occurrence of an EMR.

The presence of this EMR, whether attributed to the dawn phenomenon (3), the Somogyi phenomenon (2), or merely to the waning of insulin levels, has been repeatedly confirmed in clinical settings (3–13). The frequency of the dawn phenomenon reported previously has varied from ~0% to ~100% (3–13), depending to a great degree on patient selection and the techniques of insulin administration and dawn-phenomenon measurement. The contribution of this report is to characterize the frequency of an EMR in children who are relatively unselected with respect to age, sex, race, socioeconomic status, and duration of diabetes and who are engaged in ambulatory activities.

These findings indicate that children with midsleep CBG >200 mg/dl have relatively infrequent and sporadic rises. However, children with midsleep CBG <200 mg/dl have frequent EMRs, which often substantially perturb the constancy of early-morning glycemia. The clinical significance of the relatively high frequency of fasting rises reported here must be viewed within the context of the following additional points. Ninety percent (62 of 68) of the children with prebreakfast hyperglycemia (CBG >140 mg/dl) had a midsleep CBG of >120 mg/dl. Only 2 of these children had documented nocturnal hypoglycemia. Similarly, most (26 of 29) of the children with low to normal prebreakfast glycemia (CBG <140 mg/dl) had midsleep values >60 mg/dl. Thus, from the standpoint of that day's control, those in reasonable prebreakfast control had apparently not achieved such control at the expense of midsleep hypoglycemia, and most cases of fasting morning hyperglycemia appeared to exhibit overall insulin insufficiency. In sum, within 1 day, the dawn phenomenon alone is of minor therapeutic importance.

This conclusion, however, is not to be interpreted as mitigating the importance of these phenomena. The role of the dawn and Somogyi phenomena in perturbing early-morning control logically occurs over a time frame greater than the 2 days studied here, as the treatment of fasting morning hyperglycemia with increased evening insulin will often produce episodes of nocturnal hypoglycemia and perhaps rebound early-morning hyper-

glycemia before achieving early-morning control. Combined with the difficulty of traditional schemes of insulin administration to provide adequate insulinemia in the early-morning hours and the clinically important between-day variability in level of midsleep glycemia, these phenomena thus probably explain the tendency for the early morning to be the period of most difficult control in those with IDDM receiving traditional split-mixed insulin regimens. Furthermore, as a consequence, for certain patients using traditional split-mixed insulin regimens, avoiding hypoglycemia means accepting higher-than-desired prebreakfast glycemia.

The following can be concluded for children with characteristics similar to those investigated. First, marked change in glycemia is a common occurrence in the early morning. Second, fasting morning hyperglycemia is most commonly associated with overnight hyperglycemia. Third, the contribution of the EMR to the fasting morning hyperglycemia is, as a rule, most relevant for those with midsleep CBG <200 mg/dl. Finally, for approximately one-third of the latter cases, a fasting morning rise >40 mg/dl does occur.

ACKNOWLEDGMENTS

We thank Jay S. Skyler and the cabin clinicians and counsellor staff of Eagle's Nest Camp for Children With Diabetes for their time and support.

This research was supported by a grant from the Diabetes Research Institute Foundation, Miami, Florida. Capillary blood glucose testing supplies and equipment were donated by Lifescan, Inc.

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