Failure of a Midnocturnal Insulin Infusion to Suppress the Increased Insulin Need for Breakfast in Insulin-dependent Diabetic Patients

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SUMMARY

Insulin requirements for meals were measured in eight insulin-dependent diabetic patients, using a closed-loop insulin infusion system. Patients required more insulin for breakfast than for an isocaloric lunch (35.7 ± 5.5 mU/kcal/3 h versus 26.9 ± 5.1 mU/kcal/3 h, $P < 0.02$) or an isocaloric supper (35.7 ± 5.5 mU/kcal/3 h versus 26.6 ± 6.6 mU/kcal/3 h, $P = 0.05$). To determine whether this insulin resistance at breakfast might be due to low basal insulin levels overnight, the insulin needs for breakfast were compared after an overnight fast (day 1) and after a midnocturnal (0200 h–0500 h) insulin infusion (day 2). Breakfast insulin requirements were similar on both days (35.7 ± 5.5 mU/kcal/3 h versus 37.7 ± 5.1 mU/kcal/3 h, P = NS).

Whereas nonobese diabetic patients required approximately 60% more insulin for breakfast than for other meals, obese diabetic patients in this study did not demonstrate insulin resistance at breakfast.

These findings provide a basis for the common clinical practice of allocating more insulin for breakfast than for other meals. The absence of an increased insulin need at breakfast in our obese patients cautions against a similar algorithm for obese diabetic patients. We postulate that growth hormone may be a cause for morning insulin resistance. DIABETES *33*:266–270, March 1984.

Clinicians have long been aware of an increased insulin requirement for breakfast, as compared with other meals, despite the usually lower calorie content of breakfast. Documentation of this phenomenon is rare, although observations suggesting it have been made in normal individuals[1-3] and in diabetic patients studied with both open-loop[4] and closed-loop[5,6] insulin infusion systems. This increased insulin requirement for breakfast has been incorporated into algorithms for the open-loop infusion system.[7,8]

No satisfactory explanation for the increased insulin requirement for breakfast exists, although it may be linked to the increased basal insulin requirements observed between 0600 h and 0900 h,[9-12] termed the "dawn phenomenon."[13]

We have documented this increased insulin need for breakfast, as compared with an isocaloric lunch and supper, in eight diabetic patients using a closed-loop (Biostator, Life Science Instruments, Elkhart, Indiana) insulin infusion system. We also considered the possibility that the prolonged, relatively low insulin state attained overnight might be associated with impaired postreceptor events, leading to decreased insulin responsiveness in the morning. Numerous investigators have noted decreased tissue responsiveness to insulin after the hypoinsulinemic state[14-17] and its correction by insulin administration. To test this hypothesis, we measured the insulin requirements for breakfast on two consecutive days. On the first study day, patients fasted overnight. On the second study day, we interrupted the overnight fast by giving a midnocturnal intravenous (i.v.) infusion of glucose, accompanied by an appropriate insulin infusion via the Biostator (Life Science Instruments), to determine its effect on the breakfast insulin requirement.

MATERIALS AND METHODS

Eight insulin-dependent diabetic patients were studied at the Clinical Research Center of the Medical College of Virginia. Each patient had had at least one episode of diabetic ketoacidosis (DKA) requiring intensive care unit admission, and each was clinically judged to be a type I diabetic patient. Characteristics of the patients are listed in Table 1. Informed consent was obtained from every patient.

During the study, each patient's blood glucose was controlled with a bedside, closed-loop insulin infusion system (Biostator Glucose Controller, Life Science Instruments). Characteristics of the Biostator and its use in diabetic sub-

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TABLE 1
Characteristics of study patients

Patient	Sex	Age (yr)	DKA	Duration of diabetes (yr)	BMI*	C-peptide (ng/ml)
Nonobese						
1	M	21	Yes	16	20.8	0.51
2	F	36	Yes	14	18.0	0.32
3	M	29	Yes	9	22.2	NM†
4	F	54	Yes	20	22.2	0.26
5	M	36	Yes	6	21.2	NM†
Obese						
6	M	33	Yes	7	30.5	NA‡
7	F	33	Yes	1	27.9	0.77
8	F	30	Yes	2	34.6	0.32

*Body Mass Index (BMI) = weight in kilograms divided by the square of the height in meters. BMI of 25 corresponds closely to 120% desirable body weight.
†NM = nonmeasurable (<0.25 ng/ml).
‡NA = not available.

jects have been described previously.[5] Long-acting insulin was withheld and only regular insulin administered for 41 h before the initiation of the study. Each patient's blood glucose concentration was normalized by the Biostator during a 7-h equilibration period (1800 h–0100 h) preceding the study. Insulin was administered via the Biostator according to standard i.v. algorithms, with constants KR = 165, KF = 45, QI = 30, BI = 110, and RI = 14.

The study consisted of a 35-h period (day 1, 0100 h–day 2, 1200 h), during which patients were constantly connected to the Biostator and the blood glucose concentrations and amounts of insulin infused were recorded at minute intervals.

The diet consisted of 30 kcal/kg distributed as three isocaloric meals at breakfast (0900 h), lunch (1200 h), and supper (1800 h). Each meal contained 45% carbohydrate, 35% fat, and 20% protein. No snacks were given.

On day 1 patients had been kept fasting from 1800 h the night before, and were maintained euglycemic by the Biostator. Breakfast was then given at 0900 h. On day 2 an i.v. infusion of 50 g dextrose was administered from 0200 h–0300 h, with an accompanying machine-controlled infusion of insulin via the Biostator. The amounts of insulin infused from 0200 h to 0500 h (16–56 U) were usually equal to or greater than the amounts infused for lunch or supper. Breakfast was then again given at 0900 h. Insulin needs for each meal were calculated by measuring the total amount of insulin infused by the Biostator during the 3 h after the start of a meal.

C-peptide measurements were done on random samples by Nichols Institute (normals: 0.5–2.0 ng/ml).

Statistical analyses were performed using the Student's paired *t* test when comparing insulin requirements for meals, and Student's unpaired *t* test for all other data. All results are reported as mean ± 1 SE.

RESULTS

Insulin requirements for meals. A comparison of insulin requirements for all four meals studied (day 1: breakfast, lunch, supper; day 2: breakfast) is shown in Table 2. Insulin requirements were significantly greater for breakfast than for lunch or supper, whereas the insulin requirements for lunch and supper were similar.

Despite substantial midnocturnal infusions of insulin on day 2 (16–56 U), comparable to amounts infused for a meal, the insulin requirements for breakfast on day 1 and breakfast on day 2 were similar.

Dawn phenomenon. Examination of mean insulin infusion rates on day 1 demonstrated a substantial increase from 0600 h to 0900 h versus 0100 h to 0600 h (30 ± 4 mU/kg/h versus 20 ± 3 mU/kg/h, $P < 0.05$) (Table 3). Despite this increase in mean insulin infusion rates from 0600 h to 0900 h, there was a significant rise in mean blood glucose concentrations during this time period (Table 4).

Nonobese versus obese groups. At the end of the study, it became clear that the insulin requirement patterns were different in the nonobese (patients 1–5) and the obese (patients 6–8) type I diabetic patients. The obese patients failed to demonstrate an increased insulin requirement for breakfast when compared with lunch and supper (Tables 2 and 5).

When the obese patients were removed from analysis, the increased mean insulin requirement for breakfast compared with the other meals was even more impressive (Table 5). The nonobese group required approximately 60% more insulin for breakfast than for either lunch or supper, whereas the obese group required only 16% more insulin for breakfast than for lunch and had almost identical insulin requirements for breakfast compared with supper. The possibility that the small number of obese type I diabetic patients studied could have obscured an increase in insulin requirements at breakfast in the obese group cannot be totally excluded. The midnocturnal infusion of insulin on day 2 did not significantly alter the mean insulin requirement for breakfast on day 2 in either the nonobese or obese group.

In the nonobese group, there was a highly significant rise

TABLE 2
Insulin requirements (mU/kcal/3 h) for four isocaloric meals and effect of midnocturnal glucose and insulin infusions on breakfast insulin requirements in eight insulin-dependent diabetic patients*

Patient	1	2	3	4	5	6	7	8	$\bar{x}$ ± SEM
Breakfast (day 1)	36.5	25.0	24.7	37.7	25.1	70.0	26.9	39.5	35.7 ± 5.5†
Lunch	21.8	13.4	12.5	19.7	30.4	58.9	20.9	38.1	26.9 ± 5.1
Supper	14.8	15.9	14.3	23.0	26.2	70.6	31.0	32.9	26.6 ± 6.6
Breakfast (day 2)	40.8	25.1	36.9	34.0	32.2	70.8	34.6	26.8	37.7 ± 5.1‡

*Patients were fasting for at least 14 h before breakfast on day 1, and received midnocturnal infusions of glucose (0200 h–0300 h) and insulin (0200 h–0500 h) before breakfast on day 2 (see METHODS). Since blood glucose concentrations at the start of lunch had not uniformly returned to baseline from breakfast, it may be more appropriate to compare the insulin needs of breakfast with those of supper.
†$P < 0.02$ when compared with lunch, $P = 0.05$ when compared with supper, and P = NS when compared with breakfast on day 2.
‡$P < 0.05$ when compared with lunch, $P < 0.05$ when compared with supper, and P = NS when compared with breakfast on day 1.

TABLE 3
Hourly insulin infusion rates (mU/kg/h) and mean insulin infusion rates (mU/kg/h ± SE) on day 1 from 0100 h to 0600 h and from 0600 h to 0900 h in eight insulin-dependent diabetic patients

Patient	1	2	3	4	5	6	7	8	$\bar{x}$ ± SEM
0100–0200	26	4	9	17	28	71	2	12	
0200–0300	23	5	18	42	6	35	1	9	
0300–0400	28	28	4	49	21	31	1	5	
0400–0500	26	61	4	8	62	13	2	5	
0500–0600	42	26	4	20	4	27	3	6	
$\bar{x}$: 0100–0600	29 ± 3	25 ± 10	8 ± 3	27 ± 8	24 ± 10	35 ± 10	2 ± 1	7 ± 1	20 ± 3*
0600–0700	27	38	49	68	41	22	11	3	
0700–0800	38	20	15	17	16	44	38	7	
0800–0900	15	40	18	49	64	50	15	23	
$\bar{x}$: 0600–0900	27 ± 7	33 ± 6	27 ± 11	45 ± 15	40 ± 14	39 ± 9	21 ± 8	11 ± 6	30 ± 4*

*Statistically significant, $P < 0.05$.

in mean blood glucose concentration on day 1 from 0600 h to 0900 h when compared with 0100 h to 0600 h (120 ± 2 mg/dl versus 109 ± 3 mg/dl, $P < 0.005$), despite a significantly increased mean insulin infusion rate during this time period (34 ± 5 mU/kg/h versus 23 ± 4 mU/kg/h, $P < 0.05$). These phenomena were less apparent in the obese group, although the small number of patients in the obese group may have obscured a significant difference.

DISCUSSION

This investigation documents the increased requirement for insulin at breakfast in diabetic patients. Whereas the amounts of insulin required for an isocaloric lunch and supper were similar, approximately 40% more insulin was required at breakfast than for other meals (Table 2). Considering the current interest in the dawn phenomenon (increased basal insulin requirements from 0600 h to 0900 h), the increased insulin need for breakfast perhaps is not surprising. Both phenomena may be linked to a common cause of morning insulin resistance. Indeed, our patients required a 50% increase in basal insulin infusion from 0600 h to 0900 h, as compared with 0100 h to 0600 h (Table 3).

Not all of our patients exhibited an increased insulin requirement at breakfast. It became apparent that the absence of such a phenomenon correlated with obesity, with all three of the obese patients failing to demonstrate an increased insulin need for breakfast compared with supper (Table 2). In addition, only one of the three obese patients manifested the anticipated basal insulin resistance of obesity, as assessed by basal insulin infusion rates (Table 3). Surprisingly, recent evidence suggests that many obese diabetic patients may not demonstrate such insulin resistance.[18] Although all of our patients met the present criteria for type I diabetes, we considered the possibility that the obese patients may have had greater endogenous insulin release, which may have obscured detection of an increased morning insulin requirement. Although C-peptide measurements in patients with insulin antibodies (all patients in our study) may not always be an accurate reflection of endogenous insulin release, we determined plasma C-peptide levels in an attempt to identify those patients who might have substantial endogenous insulin secretion. C-peptide measurements failed to differentiate the obese group from the nonobese group (Table 1).

Since hypoinsulinemia has been shown to result in postreceptor insulin resistance,[14–17] we postulated that the prolonged low basal insulin state overnight might be the cause of morning resistance. To test this hypothesis, we compared the insulin requirements for breakfast on day 1 (fasting after supper the night before) and breakfast on day 2 (after a midnocturnal insulin infusion), and found no difference (Tables 2 and 5). The midnocturnal infusions of insulin were substantial (comparable with amounts infused for lunch or supper) and prolonged (from 0200 h to 0500 h), and would have been expected to correct any postreceptor resistance due to hypoinsulinemia.

TABLE 4
Mean hourly blood glucose concentrations (mg/dl) and mean blood glucose concentrations (mg/dl ± SE) on day 1 from 0100 h to 0600 h and from 0600 h to 0900 h in eight insulin-dependent diabetic patients

Patient	1	2	3	4	5	6	7	8	$\bar{x}$ ± SEM
0100–0200	121	90	107	113	105	168	93	123	
0200–0300	117	93	105	122	92	132	87	111	
0300–0400	122	112	99	123	99	126	91	105	
0400–0500	118	127	91	101	121	112	94	104	
0500–0600	124	122	94	111	96	128	98	105	
$\bar{x}$: 0100–0600	120 ± 1	109 ± 7	99 ± 3	114 ± 4	103 ± 5	133 ± 9	93 ± 2	110 ± 4	110 ± 3*
0600–0700	118	122	132	131	134	116	110	103	
0700–0800	115	108	116	113	117	130	117	107	
0800–0900	110	119	114	119	139	139	120	116	
$\bar{x}$: 0600–0900	114 ± 2	116 ± 4	121 ± 6	121 ± 5	130 ± 7	128 ± 7	116 ± 3	109 ± 4	119 ± 2*

*Statistically significant, $P < 0.02$.

TABLE 5
Mean insulin requirements (mU/kcal/3 h ± SEM) for four isocaloric meals and effect of midnocturnal glucose and insulin infusions in all study patients (patients 1–8), the nonobese group (patients 1–5), and the obese group (patients 6–8)*

	All patients (N = 8)	Nonobese group (N = 5)	Obese group (N = 3)
Breakfast (day 1)	35.7 ± 5.5	29.8 ± 3.0	45.7 ± 13.0
Lunch	26.9 ± 5.5	19.6 ± 3.3	39.3 ± 11.0
Supper	26.6 ± 6.6	18.8 ± 2.5	44.8 ± 12.9
Breakfast (day 2)	37.7 ± 5.1	33.8 ± 2.7	44.1 ± 13.6

*Patients were fasting for at least 14 h before breakfast on day 1, and received midnocturnal infusions of glucose (0200 h–0300 h) and insulin (0200 h–0500 h) before breakfast on day 2 (see METHODS).

Some investigators had postulated that elevations of counterregulatory hormones may account for morning insulin resistance, but to date there is little evidence to support this contention. It has been demonstrated that glucagon levels are not elevated during the morning hours.[9,19] Bright et al.[19] observed that cortisol blockade with metyrapone failed to suppress the dawn phenomenon. This would suggest that the diurnal secretion of cortisol is not the primary mechanism for morning insulin resistance. Also, the diurnal secretion of cortisol would not explain the lack of morning resistance found in our obese group. Catecholamines would appear to be unlikely candidates to cause the dawn phenomenon, since catecholamine levels are low during sleep.[20] One study of the dawn phenomenon showed no increase in catecholamine levels during the period of morning insulin resistance.[21]

Growth hormone (GH) remains a possible cause for morning insulin resistance. Growth hormone antagonizes the effects of insulin at a postreceptor level.[22] Peak secretion of GH occurs 1–2 h after the onset of sleep,[23] and its insulin-antagonistic effects are usually delayed for 2–12 h.[24] In addition, the clearance of GH is decreased in diabetic patients.[25,26] Therefore, morning insulin resistance could conceivably be a manifestation of GH secreted hours earlier.

The intriguing observation that our obese patients did not exhibit morning insulin resistance could be the result of the blunted nocturnal secretion of GH in obese patients.[27] Some investigators have proposed that this may be due to elevated free fatty acid levels in obese persons.[28] Further studies are needed to elucidate the possible role of GH in the increased requirement for insulin at breakfast and in the dawn phenomenon.

It should be emphasized that the results of this study would support the clinical practice of allocating more insulin to cover the breakfast meal in nonobese diabetic patients, since our nonobese patients required approximately 60% more insulin for breakfast than for other meals (Table 5). However, this study also would caution against doing so in all diabetic patients, particularly in those with obesity, since these patients failed to demonstrate an increased insulin need for breakfast (Table 5). Such a practice could lead to hypoglycemia in some patients.

The rise in mean blood glucose concentrations on day 1 from 0600 h to 0900 h (Table 4), despite concomitant increases in mean insulin infusion rates during this period, demonstrates the present limitations of a closed-loop infusion system for clamping studies. Given this and other technical difficulties (such as hourly pertubations in basal insulin needs even within an individual patient) that we and others[18,29] have encountered when attempting to measure the dawn phenomenon accurately, it may be that examination of the increased insulin requirement for breakfast should be the preferred method of studying the phenomenon of morning insulin resistance.

Finally, with increasing use of multiple injections of rapid-acting insulin before meals and insulin pump therapy delivering boluses of insulin before meals, the utility of the closed-loop insulin infusion system in predicting the insulin requirements for meals warrants further investigation. This may be especially important given the large intermeal variations in insulin requirements found in this study.

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