Effect of Temporal Distribution of Calories on Diurnal Patterns of Glucose Levels and Insulin Secretion in NIDDM

Christine A. Beebe, MS, RD
Eve Van Cauter, PhD
E. Timothy Shapiro, MD
Hartmut Tillil, MD
Rachel Lyons, MS, RD
Arthur H. Rubenstein, MD
Kenneth S. Polonsky, MD

The effect of different temporal patterns of calorie intake on plasma glucose, serum insulin, and insulin secretion rates was examined in six patients with moderately well controlled non-insulin-dependent diabetes mellitus (NIDDM). Patients were studied on three separate occasions over 26 h. Total calories and food composition (50% carbohydrate, 15% protein, and 35% fat) were kept constant, but the pattern of calorie intake was varied. In study A (similar meal size), calories were distributed as 30, 40, and 30% at breakfast, lunch, and dinner, respectively. In study B (3 snacks, 3 meals), each subject ate three meals of 20, 20, and 30% of calories for breakfast, lunch, and dinner, respectively, and three snacks, each comprising 10% of calories, presented 2.5 h after the meal. In study C (large dinner), 10% of calories were consumed at breakfast, 20% at lunch, and 70% at dinner. Glucose, insulin, and C-peptide concentrations were measured at 15- to 30-min intervals. Insulin secretion rates were calculated from C-peptide levels with individually derived C-peptide clearance parameters. The different eating patterns were associated with only modest differences in overall levels of glucose and insulin secretion. Daytime insulin secretion was lowest when most of the daily calorie intake occurred in the form of a large dinner. Overnight levels of glucose and insulin secretion rates did not differ for the three eating patterns, and the morning glucose levels were also unaffected by the pattern of calorie intake on the previous day. A morning rise of glucose of >0.28 mM occurred consistently only when dinner was of moderate size (30% of total calories).

We conclude that if total calorie content and food composition are kept constant, overall blood glucose control is only modestly affected by the temporal pattern of food intake. The partition of food intake into meals and snacks does not improve glucose control, and a large dinner does not result in significantly higher overnight or next-morning glucose levels. *Diabetes Care* 13:748–55, 1990

From the Department of Medicine, University of Chicago, Chicago, Illinois; and the Institute of Interdisciplinary Research, Free University of Brussels, Brussels, Belgium.

Address correspondence and reprint requests to Kenneth S. Polonsky, MD, University of Chicago, Department of Medicine, Box 435, 5841 South Maryland Avenue, Chicago, IL 60637.

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Although a hypocaloric diet with weight loss is the primary nutrition plan for most overweight individuals with non-insulin-dependent diabetes mellitus (NIDDM), it has also been suggested that altering the composition of the diet and the intervals between meals may have a significant effect on blood glucose control (1–4). The existence of diurnal variations in glucose and insulin responses to meals of equal composition further suggests that the timing of food intake may influence blood glucose homeostasis (5–7). An eating pattern consisting of small meals with snacks between meals is often thought to be advantageous as far as glucose control is concerned (8,9). In contrast, the eating patterns of many obese subjects, who consume most of their daily calorie intake in the latter part of the day, are thought to foster hyperglycemia (8–11). Whether such differences in temporal distribution of calories are associated with quantitative alterations in glucose levels and insulin secretion, which may be of clinical relevance, has not been systematically studied in a controlled fashion.

In this study, the effect of three different temporal patterns of calorie intake on peripheral levels of glucose, insulin, and C-peptide was examined for 26 h in six patients with moderately well controlled NIDDM. The

TABLE 1
Patient characteristics

Subject	Sex	Age (yr)	Body mass index (kg/m²)	HbA_{1c} (%)	Treatment
1	M	52	29	6.89	Diabenase (250 mg/day)
2	F	47	37	10.08	Glucotrol (30 mg/day)
3	M	52	28	8.46	Diet
4	F	52	31	9.96	Glyburide (5 mg/day)
5	M	35	58	8.81	Micronase (10 mg/day)
6	M	64	33	9.13	Glyburide (5 mg/day)
Mean ± SE		50 ± 4	35 ± 5	8.9 ± 0.5	

total number of calories and food composition were maintained constant. Quantitative estimates of insulin secretion were derived by calculation from plasma C-peptide levels with individually measured parameters for C-peptide clearance.

RESEARCH DESIGN AND METHODS

Six subjects with NIDDM were studied. Their clinical characteristics are given in Table 1. Their mean fasting blood glucose, measured at 0700 on 3 different days, ranged from 5.72 to 9.97 mM. HbA_{1c} was measured by affinity chromatography and was ≤10% in all subjects (normal <6.5%). None of the patients were treated with insulin. Patients taking oral hypoglycemic agents remained on their prescribed dose throughout the study. Studies were performed in the Clinical Research Center of the University of Chicago after written informed consent was obtained. The experimental protocol was approved by the institutional review board.

Subjects were studied on three separate occasions for 26 h beginning at 0700 and ending at 0900 the next morning. They were admitted the night before each study and ate a standard meal at 1800 consisting of 40% of total daily calorie requirements. No food was allowed between this evening meal and 0700, which represented the beginning of the study. During each 26-h study, subjects consumed a diet consisting of 50% carbohydrate, 15% protein, and 35% fat. This ratio was maintained at all meals and snacks. Identical foods were used on all three occasions to minimize variations in the glycemic response to individual foods (12,13). Foods were obtained from the hospital's dietary department. Meal composition is given in Table 2. Resting basal metabolic rate was determined for each patient with a ventilated hood open-circuit gas exchange system, described in detail elsewhere (14). Daily calorie intake was calculated as 20% above the calculated resting calorie requirement.

During each of the three 26-h periods, the total number of calories and macronutrient composition was maintained constant but the pattern of calorie intake was varied. In study A (similar meal size), calories were distributed as 30, 40, and 30% at breakfast, lunch, and dinner, respectively. In study B (3 meals, 3 snacks), each subject ate three meals of 20, 20, and 30% of calories for breakfast, lunch, and dinner, respectively, and three snacks, each comprising 10% of calories, presented 2.5 h after the meal. In study C (large dinner), 10% of calories were consumed at breakfast, 20% at lunch, and 70% at dinner. Meals were presented at 0800, 1300,

TABLE 2
Meal constituents

			Snacks (study C)		
Breakfast	Lunch	Dinner	Morning	Afternoon	Evening
Whole-wheat toast	Turkey	Grape juice	Peanut butter	Cheese	Ham
Scrambled egg	White bread	Vegetable soup	White bread	Saltines	White bread
Margarine	Mustard	Saltines	Orange juice	Apple juice	Mayonnaise
Diet jelly	Potato chips	Hamburger (20% fat)			Grape juice
Orange juice	Apple juice	Hamburger bun			
Decaffeinated coffee	2% Milk	Ketchup			
	Vanilla wafers	Corn			
		2% Milk			
		Vanilla ice cream			
		Apple pie			

and 1800 and were consumed within 30 min. Blood samples for glucose, insulin, and C-peptide were collected from an indwelling catheter at 15- to 30-min intervals throughout the 26-h study. The studies were performed at 2-wk intervals, and their order was randomized.

In addition, each subject participated in a morning outpatient study designed to determine the individual kinetics of C-peptide clearance. The details of this protocol have been published previously (15). Briefly, after an overnight fast, endogenous insulin secretion was suppressed by a primed somatostatin infusion (550 μg/h), and a bolus intravenous injection of 150 μg biosynthetic human C-peptide (Lilly, Indianapolis, IN) was administered. Peripheral C-peptide concentrations were measured at frequent intervals for 3 h after the C-peptide injection.

Blood samples for insulin were allowed to clot at room temperature and the serum was stored at −20°C until assayed. The C-peptide samples were drawn into tubes at 4°C containing 500 KIU/ml trasylol and 1.2 mg/ml EDTA. Plasma was immediately separated and stored frozen until assayed. Serum insulin was assayed by a double-antibody technique (16). Plasma C-peptide was measured as previously described (17). Plasma glucose was determined by the glucose oxidase technique (Beckman glucose analyzer, Fullerton, CA).

Insulin secretion rates were derived by mathematical analysis from peripheral C-peptide concentrations with a two-compartment model for C-peptide distribution and clearance. For each individual, the metabolic clearance rate and fractional rate constants for C-peptide were calculated from the decay curve of C-peptide observed after bolus intravenous injection of biosynthetic human C-peptide (15). Nonlinear least-squares regression analysis of C-peptide decay curves was performed with the BMDP 3R program (Los Angeles, CA). The rate constants measured were applied to the endogenous plasma C-peptide concentrations measured during the 26-h meal studies, and individual insulin secretion rates were derived (15). Mean values for the rate constants K_1, K_2, and K_3 were 0.079 ± 0.01, 0.061 ± 0.009, and 0.064 ± 0.049 min^{-1}, respectively, and mean volume of distribution was 5172 ± 375 ml.

The fasting levels of glucose and insulin secretion rates were defined as the mean levels between 0700 and 0800. Daytime levels of glucose and insulin secretion rates were calculated as the mean levels during the 16-h interval between 0800 and midnight. For the remainder of the study (midnight to 0900), mean levels of glucose and insulin secretion rates were calculated for the early night (midnight to 0300), late night (0300–0600), and morning (0600–0900).

Statistical tests. Results are expressed as means ± SE. Individual values were compared by analysis of variance measures (Statistical Analysis System, SAS Inst., Cary, NC) and the Wilcoxon test for pairwise contrasts in the nonparametric analysis of variance for repeated measures (18).

RESULTS

Figure 1 shows the mean profiles of plasma glucose, serum insulin, and insulin secretory rates observed in the three study conditions. Fasting levels of glucose, insulin, and insulin secretion rates did not differ significantly across studies (Table 3). Mean values for the peak levels of glucose, insulin, and insulin secretion rates after each meal are listed in Table 4. The three different patterns of calorie distribution resulted in differences in the magnitude and temporal organization of changes in glucose levels and insulin secretory rates. In studies A (3 meals of similar size) and B (3 meals, 3 snacks), despite the fact that glucose levels returned to baseline between meals, insulin secretory rates did not return to fasting levels until 5 h after dinner. In contrast, when both breakfast and lunch were meals of small size (study C), insulin secretory rates returned to fasting levels between meals. The sharp meal-induced peaks and preprandial troughs of glucose and insulin secretion rate in study A were blunted in study B, where the major effect of the snacks was to prolong the response to the previous meal and delay the return to premeal levels.

A more detailed inspection of the data reveals that the responses to meals containing identical calorie loads are influenced by meal spacing and time of day.

The effects of spacing between meals were most evident when comparing the response to an intake of 10% of total daily calories taken either as a breakfast meal (as in study C) or as a snack presented 2.5 h after breakfast (as in study B). After the morning snack ingested in study B (Figs. 1 and 2, *middle panels*), glucose levels increased by only 0.71 ± 0.24 mM compared with 3.86 ± 0.56 mM when the same amount of calories were ingested after an overnight fast in study C ($P < 0.01$). Minimal increments in insulin secretion were observed after the postbreakfast snack (averaging 25 ± 18 pmol/min), whereas intake of the same number of calories at breakfast elicited a well-defined secretory response of larger magnitude (233 ± 38 pmol/min, $P < 0.01$).

An effect of time of day was apparent when the responses to 30% calories eaten at breakfast were compared with responses to 30% of calories eaten at dinner in study A. Premeal glucose levels were similar at both times of meal presentation (Figs. 1 and 2, *left panels*). Glucose levels declined more rapidly in the morning (premeal levels were reached 213 ± 24 min after the meal) than in the evening (premeal levels did not resume until 310 ± 30 min after the meal; $P < 0.05$).

The mean levels of glucose and insulin secretion during the daytime (0800 to midnight) in the three studies are shown as absolute values in the left panels of Fig. 3 and as increments above fasting levels in the right panels of Fig. 3. Absolute glucose levels were 10–15% higher when three meals and three snacks were ingested in study B than in studies A and C ($P < 0.05$). This slight increase in mean glucose levels associated with the

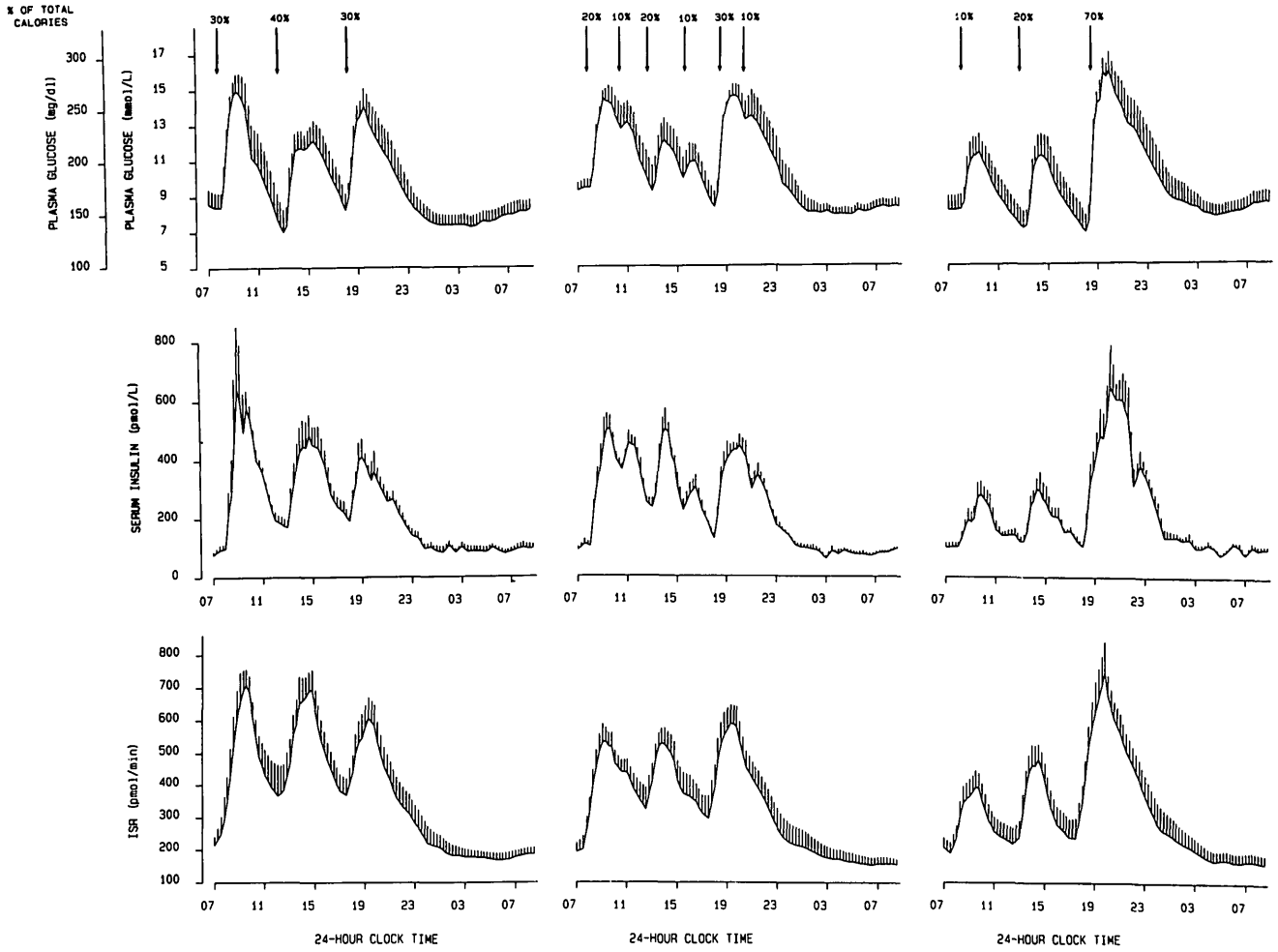

FIG. 1. Profiles of plasma glucose (*top*), serum insulin (*middle*), and insulin secretion rates (ISRs) (*bottom*) during 3 study conditions. *Arrows*, proportion of total calories for each meal and its time of presentation. *Left panels*, study A (30% of total calories at dinner); *middle panels*, study B (30% + 10% of total calories at dinner); *right panels*, study C (70% of total calories at dinner). Values are means ± SE.

splitting of calorie intake into meals and snacks was accompanied by overall levels of insulin secretion that were significantly lower ($P < 0.02$) than in study A, when the daily calorie intake was distributed into three meals of similar size without snacks. Absolute glucose levels and insulin secretory rates were lower in study C (large dinner) than in study B (meals and snacks; $P < 0.02$), reflecting the maintenance of near or below fast-

TABLE 3
Fasting and next-morning levels of glucose and insulin secretion rates (ISRs)

	Study A (3 meals of similar size)	Study B (3 meals, 3 snacks)	Study C (large dinner)
Fasting (0700–0800)			
Glucose (mM)	8.44 ± 0.89	9.44 ± 0.44	8.10 ± 0.89
Insulin (pM)	98 ± 13	136 ± 37	149 ± 49
ISR (pmol/min)	233 ± 38	191 ± 33	198 ± 34
Next morning (0600–0900)			
Glucose (mM)	8.05 ± 0.61	8.22 ± 0.44	8.22 ± 0.67
Insulin (pM)	133 ± 43	132 ± 32	132 ± 34
ISR (pmol/min)*	194 ± 37	157 ± 22	166 ± 29

Values are means ± SE.
*$P < 0.05$ interstudy difference. All others NS.

TABLE 4
Peak glucose, insulin, and insulin secretion rates (ISRs) after meal ingestion

	Breakfast			Lunch			Dinner		
	Study A	Study B	Study C	Study A	Study B	Study C	Study A	Study B	Study C
Glucose (mM)	15.5 ± 0.9	15.4 ± 0.8	12.0 ± 1.2*†	13.0 ± 1.1	12.4 ± 1.2	11.6 ± 1.3	14.4 ± 1.2	15.7 ± 0.9	16.4 ± 1.0
Insulin (pM)	1.069 ± 322	674 ± 105*	423 ± 105*†	839 ± 310	696 ± 152	502 ± 135	732 ± 287	617 ± 114	854 ± 143
ISR (pmol/min)	781 ± 60	577 ± 50*	433 ± 53*†	751 ± 60	547 ± 49*	524 ± 47*	617 ± 66	615 ± 62	776 ± 88

Values are means ± SE. Study A, calories distributed as 30, 40, and 30% at breakfast, lunch, and dinner, respectively; study B, calories distributed as 20, 20, and 30% at breakfast, lunch, and dinner, respectively, and 3 snacks of 10% of calories; study C, calories distributed as 10, 20, and 70% at breakfast, lunch, and dinner, respectively.
*P at least <0.05 from study A.
†P at least <0.05 from study B.

ing levels during significant portions of the daytime. Differences in mean daytime levels of plasma insulin between the three study conditions followed the same pattern as insulin secretory rates (study A, 515 ± 204 pM; study B, 425 ± 101 pM; study C, 375 ± 101 pM). When fasting values were subtracted from daytime levels, interstudy differences were nonsignificant for glucose but were similar to those observed for the absolute values for insulin secretion rates (Fig. 3, *right panels*).

Regardless of the temporal distribution of calorie intake, mean levels of glucose and insulin secretion rates in the early (midnight to 0300) and late (0300–0600) hours of the night were similar in the three studies. Furthermore, morning glucose levels measured between 0600 and 0900 were also unaffected by the pattern of food intake during the preceding day (Table 3). Morning insulin secretion rates were 15–25% higher in study A when the last meal was an average-size dinner (30% of total calories) eaten early in the evening. Figure 1 shows that insulin secretion rates fell continuously throughout the night to reach morning levels that were significantly lower than the day before at the same time. The pattern of change in glucose levels and insulin secretory rates during the night is shown in more detail in Fig. 3. Glucose levels declined during the early part of the night but then started increasing again in the later part of the night, at a time consistent with previous descriptions of the dawn phenomenon in NIDDM (19). In study A (last meal at 1800 with 30% of total daily calories), mean glucose levels increased by at least 0.28 mM between

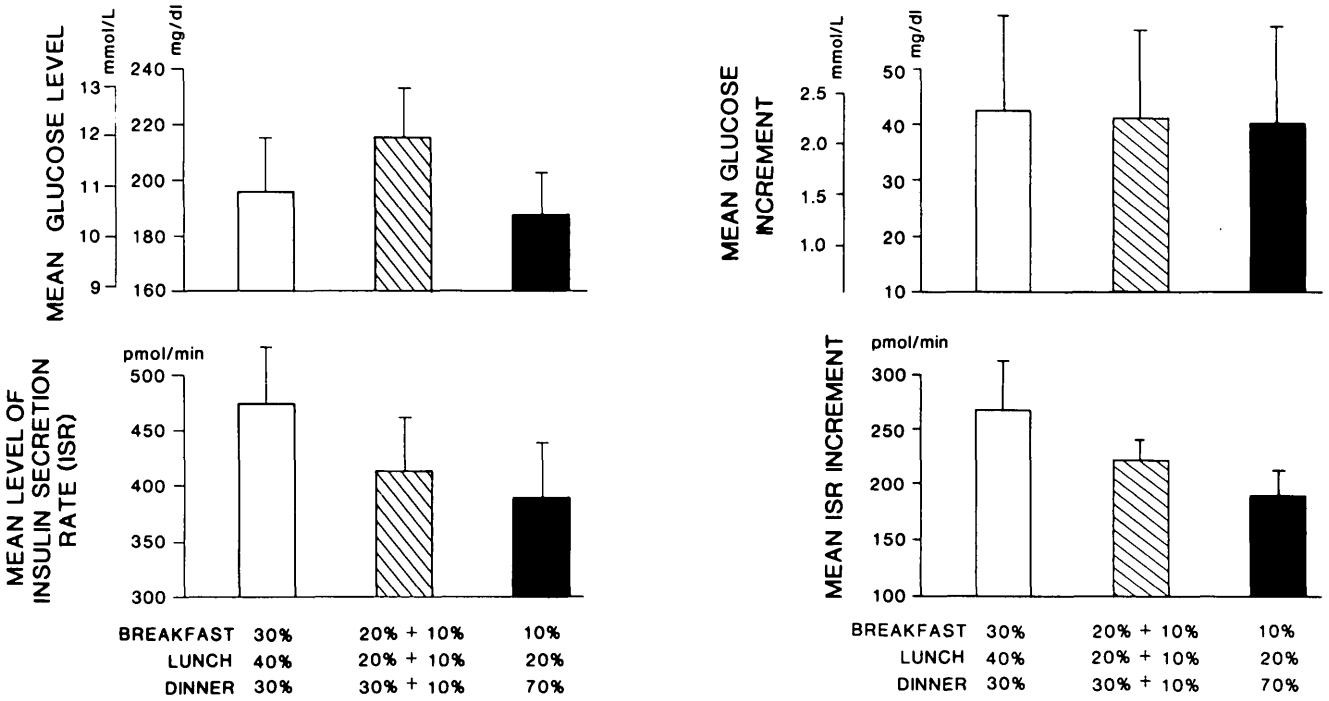

FIG. 2. Glucose levels (*upper left panel*) and glucose increments above fasting levels (*upper right panel*) for 3 study conditions. Insulin secretory rates (ISRs) (*lower left panel*) and increments in secretory rate above fasting levels (*lower right panel*) for study A (3 meals of similar size, *open bars*), study B (3 meals, 3 snacks, *hatched bars*), and study C (large dinner, *solid bars*). Values are means ± SE.

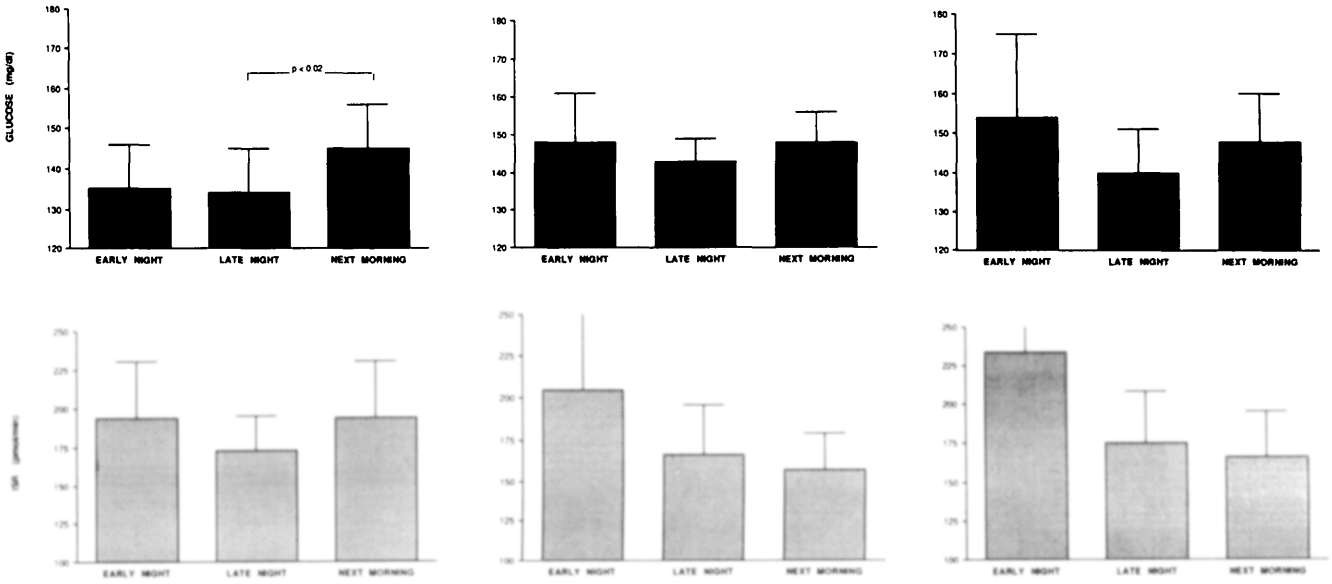

FIG. 3. Levels of blood glucose and insulin secretory rates (ISRs) in 3 study conditions in early part of night (midnight to 0300), late part of night (0300–0600), and morning (0600–0900). Differences between late part of night and morning are significant for glucose in study A. *Left panels*, study A (30% of total calories at dinner); *middle panels*, study B (30% + 10% of total calories at dinner); *right panels*, study C (70% of total calories at dinner). Values are means ± SE.

the late night (0300–0600) and the morning (0600–0900) in all subjects ($P < 0.02$). In studies B (snack at 2030 with 10% of total daily calories) and C (dinner at 1800 with 70% of total daily calories), morning glucose levels were at least 0.28 mM higher than late-night glucose levels in three of six patients and four of six patients, respectively.

DISCUSSION

It is assumed that equal distribution of calories throughout the day optimizes glucose control and enhances weight-reduction efforts (1,4,6,8–11). The eating pattern of many obese individuals, i.e., little or no breakfast, a small lunch, and a large meal consumed late in the day, is believed to predispose a person to glucose intolerance (8,11). Indeed, in healthy subjects glucose tolerance decreases as the day progresses and reaches a minimum around the middle of the sleep period (20,21). This diurnal variation is reflected in larger glucose responses to mixed meals or oral glucose loads in the late afternoon and evening rather than in the morning (5–7,22). Thus, an even distribution of calories, with both breakfast and lunch of similar size as dinner, would be expected to improve glucose tolerance. Eating 3 meals/day, preferably with small snacks between meals, is frequently recommended to optimize glucose control in both insulin-dependent diabetes mellitus and NIDDM patients (1,8). This study was designed to quantitate the effects of varying the temporal pattern of food intake on daily glucose concentrations and insulin secretion in diabetic patients. The results show that widely different eating patterns are associated with only modest variations in overall levels of glucose concentrations and insulin secretion and that the splitting of daily calorie intake into meals and snacks does not improve overall glucose control. Moreover, the consumption of most of the daily calorie intake in the form of a large dinner does not appear to significantly raise glucose levels overnight or the next morning as long as the total daily calorie load is not increased.

Surprisingly, the regimen of 10% of calories at breakfast, 20% at lunch, and 70% at dinner did not adversely affect the next morning's glucose concentrations, which were not significantly different from those measured after the other two eating patterns. Thus, the belief that the size of the dinner influences the next morning's fasting glucose levels was not confirmed in this study. This feeding regimen was also associated with the lowest daytime levels of insulin secretion. In the absence of major differences in blood glucose, it is possible that lower insulin secretion may be beneficial because high insulin levels are related to increased cardiovascular disease. In summary, we were unable to find experimental evidence for adverse effects on overall glucose levels from concentrating most of the calorie intake in the later part of the day.

Responses to food ingestion appeared to be modulated not only by calorie content but also by meal spacing and time of day. Widely different responses to the ingestion of 10% of total daily calories were observed when the food was presented after an overnight fast or 2.5 h after a larger meal. It is possible that, when a snack

containing 10% of total calories was consumed shortly after a previous meal, the blunted glucose and insulin responses were due to the second meal effect; i.e., residual insulin action from the first response reduced insulin requirements for the second meal (21–23). Confirming our previous observations in healthy, obese, and diabetic subjects (24–26), time of day was found to influence the duration of the glucose response to an identical calorie load presented over a similar premeal level, with longer responses in the evening than in the morning. The effects of preprandial levels and time of day will need to be considered in the design of diets aimed at minimizing hyperglycemia in conditions of impaired glucose tolerance.

In our NIDDM patients, the occurrence of an early-morning increase in plasma glucose levels, often called the dawn phenomenon, appeared to be influenced by the size and timing of the last meal on the previous day (19). An increase of glucose concentrations >0.28 mM from late sleep to early morning was consistently present only when the dinner included 30% of total calories and was given at 1800. When a late snack or a large dinner was consumed, plasma glucose levels either did not increase at dawn or the increase was of smaller magnitude. Additional studies will be needed to determine if delaying the time of dinner or ingesting a postdinner snack may be helpful in the prevention of this early-morning increase in glucose levels.

In summary, this short-term study suggest that when total calorie content and food composition are kept constant, the temporal pattern of food intake has only modest effects on overall levels of blood glucose and insulin secretion. Long-term studies will be necessary to evaluate whether cumulative effects of differences in levels of insulin secretion need to be considered in the design of optimal dietary regimens for NIDDM patients.

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