Absorption Characteristic of Breakfast Determines Insulin Sensitivity and Carbohydrate Tolerance for Lunch

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To test the hypothesis that prolonging absorption of breakfast might improve the glucose tolerance of the subsequent meal served at lunch, normal male volunteers were administered the same carbohydrate in either a rapidly absorbed (sucrose, S) or slowly absorbed (sucrose with guar, S + G) form for breakfast (0800) and lunch (1145). Area under the curve (AUC) for glucose did not differ for S at breakfast vs. S + G at breakfast, although $AUC_{insulin}$ for S at breakfast was greater than that for S + G at breakfast (3389 ± 608 vs. 1523 ± 246 μU · min · ml^{-1}, $P < .002$). Plasma glucose and insulin profiles for the two breakfast meals differed markedly. Once S was ingested, plasma glucose and insulin returned to baseline after 120 and 160 min, respectively. However, once S + G was ingested, plasma glucose and insulin were still significantly above baseline values after 180 min. When S was eaten for breakfast, $AUC_{glucose}$ for lunch was similar to that for breakfast, regardless of whether lunch consisted of S or S + G. However, if S + G was eaten for breakfast, $AUC_{glucose}$ for S + G or S at lunch was 44% ($P < .005$) and 75% of that for breakfast, respectively. Only one of five subjects who ingested S + G for breakfast failed to exhibit a fall in $AUC_{glucose}$ when S was eaten for lunch. The beneficial effect of prolonged absorption of breakfast on the glucose tolerance of lunch was not observed if the timing of lunch was delayed by 2 h (i.e., served at 1345). These observations suggest that in normal humans, prolonged absorption of breakfast results in prolonged elevation of plasma insulin levels and enhanced insulin sensitivity at lunch, thereby improving carbohydrate tolerance for lunch. ***Diabetes Care*** **11:755–60, 1988**

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Dietary management of the diabetic patient has assumed renewed importance in recent years. Nonetheless, little attention has been devoted to the clinical observation that diabetic patients require more insulin for the relatively calorie-poor breakfast meal than for lunch or supper (1,2). This is despite the fact that the increased insulin requirement for breakfast has been incorporated into algorithms for open-loop insulin infusion systems (3,4). We previously documented increased insulin need for a mixed meal at breakfast, compared with an isocaloric meal at lunch or supper, in type I (insulin-dependent) diabetic patients (1). At that time, we postulated that the increased insulin need for breakfast may be linked to increased basal insulin requirements observed between 0600 and 0900, termed the *dawn phenomenon,* and that the need may be due to morning insulin resistance. However, our recent observations have necessitated our revision of this hypothesis. In a study comparing insulin reqirements of type I diabetic patients for isocaloric amounts of a rapidly absorbed carbohydrate (sucrose) versus a slowly absorbed carbohydrate (hydrogenated corn syrup), we observed the following (5): if the rapidly absorbed carbohydrate was given for breakfast (0800) followed by the slowly absorbed carbohydrate for lunch (1300), the insulin requirements for the two meals were identical. However, if the sequence was reversed, i.e., the slowly absorbed carbohydrate was given for breakfast, followed by the rapidly absorbed carbohydrate for lunch, the insulin requirement for lunch was significantly less than for breakfast. These observations suggest that the absorption characteristic (rapidly vs. slowly absorbed) of the first meal might influence the insulin requirement for the subsequent meal and that the difference in meal insulin requirements between breakfast and lunch is not due to an intrinsic diurnal variation in insulin sensitivity.

This finding is reminiscent of the Staub-Traugott effect, which refers to the improved disposition of a second glucose load when two glucose loads are given as closely spaced challenges (6,7). Increased insulin sensitivity during the second challenge may be related to a residual insulin effect from the preceding glucose challenge (8). Thus, prolonged hyperinsulinemia following a slowly absorbed carbohydrate eaten for breakfast might promote enhanced tolerance for a second carbohydrate challenge administered 5 h later, whereas the short-lived hyperinsulinemia of a rapidly absorbed carbohydrate load might shorten the interval between carbohydrate challenges, which would enable the phenomenon to be observed. To test this hypothesis, we examined the glycemia and insulin profiles of normal men after sucrose loads were given at breakfast (0800) and lunchtime (1145), where the same carbohydrate was ingested in either a rapidly absorbed or slowly absorbed form. The test carbohydrates consisted of either sucrose (S), a rapidly absorbed carbohydrate, or sucrose with guar (S + G), a slowly absorbed carbohydrate. Guar, an unabsorbable plant polysaccharide, is known to retard the absorption rate of S without affecting the total amount absorbed (9,10). In addition, we examined the effect of increasing the time interval between breakfast and lunch by 2 h on the glucose tolerance of lunch subsequent to a slowly absorbed breakfast.

MATERIALS AND METHODS

Subjects and protocols. Six normal men, who were not taking any medications and had no family history of diabetes mellitus, participated in the study. Characteristics of the study group are detailed in Table 1. Subjects participated in five protocols (vide infra), each separated by at least 1 wk from the other and conducted consecutively. Protocols were not randomized, and it is unknown whether lack of randomization affected the results. One man (subject 6 in Table 1) withdrew after participating in protocols I–III because of gastrointestinal intolerance (nausea) to guar. Therefore, five subjects participated in protocols IV and V. The study was approved by the Committee on the Conduct of Human Research of the Medical College of Virginia, and signed consent was obtained from each subject.

TABLE 1
Anthropometric data at start of study

Subject	Age (yr)	Height (m)	Weight (kg)	Body mass index (kg/m²)	Range of weight during entire study (kg)
1	26	1.82	76.9	23.2	75.7–76.9
2	26	1.70	66.5	23.0	65.6–66.7
3	25	1.69	55.9	19.6	55.9–57.7
4	21	1.85	87.2	25.5	84.4–87.2
5	23	1.78	73.8	23.3	73.3–74.7
6	24	1.80	91.1	28.1	91.1–92.6

Subjects were admitted to the General Clinical Research Center after an overnight fast. In protocols I–IV, subjects were fed either S or S + G for breakfast at 0800 and for lunch at 1145. In protocol V, subjects were fed S + G for breakfast at 0800 and S for lunch, which was delayed by 2 h and served at 1345. The S meal consisted of 80 g sucrose (Western Sugar, Denver, CO) dissolved in 570 ml tap water and 30 ml lemon juice (DORI Foods, Richmond, VA), and the S + G meal consisted of 80 g sucrose and 23 g guar (Gumix International, Hackensack, NJ) dissolved in 570 ml tap water and 30 ml lemon juice. All test carbohydrates were ingested within 15 min of presentation.

The protocols were as follows. Protocol I: S was administered at breakfast (0800), followed by S at lunchtime (1145). Protocol II: S + G was administered at breakfast (0800), followed by S + G at lunchtime (1145). Protocol III: S was administered at breakfast (0800), followed by S + G at lunchtime (1145). Protocol IV: S + G was administered at breakfast (0800), followed by S at lunchtime (1145). Protocol V: S + G was administered at breakfast (0800), followed by S at 1345. Blood samples for plasma insulin and glucose were drawn via a heparin lock immediately before each meal (0 min) and then every 20 min for 3 h. The observation period was 3 h because it has been reported that in normal individuals a period of at least 3 h is required for insulin levels to return to baseline following an oral 50-g glucose challenge (11). Subjects were supine with the head of the bed at a 45–90° angle during each protocol. They were allowed to stand and visit the lavatory between meals.

At each study session, subjects were instructed not to alter their diet or level of activity in any way. Subjects were weighed at each session, and the largest weight variation in an individual subject during the entire study was 3.2% (Table 1).

Assays. Plasma insulin was assayed by double-antibody radioimmunoassay (12), and the lower limit of detection was 4.0 μU/ml. The intra- and interassay coefficients of variation for the insulin assay were 5 and 8%, respectively. Plasma glucose was determined by the glucose oxidase method (Glucose Analyzer 2, Beckman, Fullerton, CA). All blood samples from an individual subject during one protocol were run in the same assay. Blood samples from separate protocols were not always assayed at the same time.

Statistical analysis. Data are presented as means ± SE. Area under the curve (AUC) for glucose and insulin were determined by the trapezoidal rule using δ-values (value at *x* min − value at 0 min, where 0 min is defined as the start of a meal). The plasma glucose level sometimes fell below baseline 120 min after the ingestion of S. We believe that interpreting this fall as a negative $AUC_{glucose}$ may not be meaningful from a physiological standpoint and would falsely lower total $AUC_{glucose}$ values for the test carbohydrate. Therefore, negative δ-values were regarded as equivalent to zero. Calculation of data using negative δ-values yielded similar results.

When paired data from a single protocol were compared, the two-tailed paired Student's *t* test was utilized. When values from multiple protocols were compared, data were analyzed using PROC GLM in SAS, with a randomized block analysis of variance. This analysis takes into account the fact that a subject may be used more than once in making a comparison between test carbohydrates. $P < .05$ was considered significant.

RESULTS

Effect of guar on breakfast glucose and insulin profiles. Figure 1 displays $AUC_{glucose}$ and $AUC_{insulin}$ values for all five protocols when S (n = 12) or S + G (n = 16) was eaten for breakfast. Marked intra- and intersubject variations were noted. $AUC_{glucose}$ values for S at breakfast versus S + G at breakfast overlapped substantially and were not significantly different (4085 ± 477 vs. 2892 ± 347 mg · min · dl^{-1}, NS). The probability of type 2 error (i.e., accepting the null hypothesis when a true difference exists) is .80. The mean $AUC_{insulin}$ value for S at breakfast was greater than that for S + G at breakfast (3389 ± 608 vs. 1523 ± 246 μU · min · ml^{-1}, $P < .002$), despite considerable overlap. Unexplained is the consistently low insulin response of subject 4 in all protocols, despite normal glucose profiles. Simultaneous C-peptide determinations suggest that this subject's insulin secretory response was normal (data not shown).

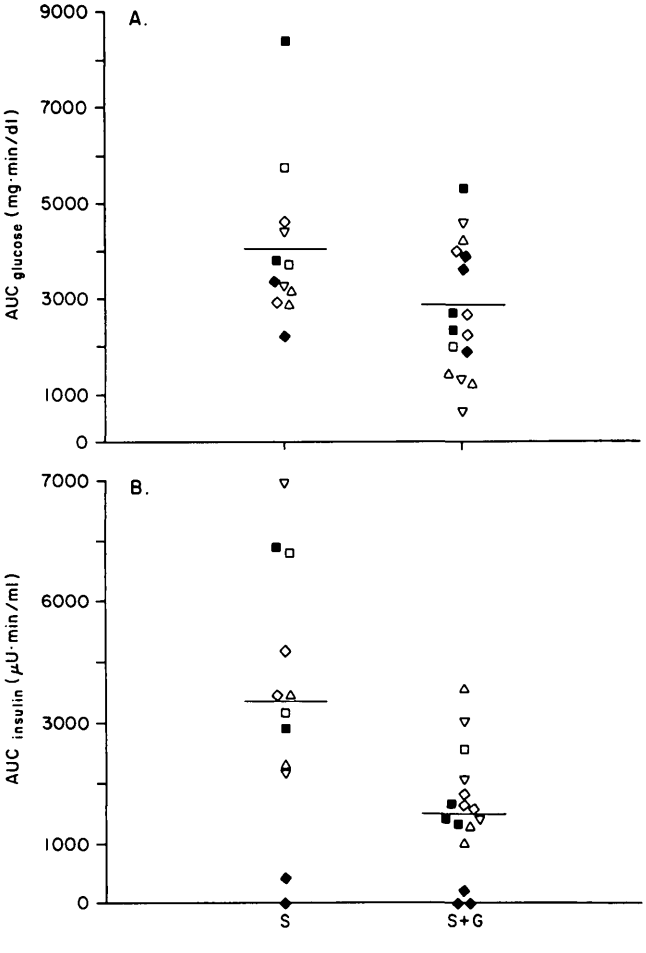

FIG. 1. Area under curve $(AUC)_{glucose}$ (*A*) and $AUC_{insulin}$ (*B*) for sucrose (S) or sucrose with guar (S + G) ingested at breakfast at 0800; n = 12 for S meals, and n = 16 for S + G meals. *Horizontal bars* represent mean values. ▽, Subject 1; ◇, subject 2; △, subject 3; ♦, subject 4; ■, subject 5; □, subject 6.

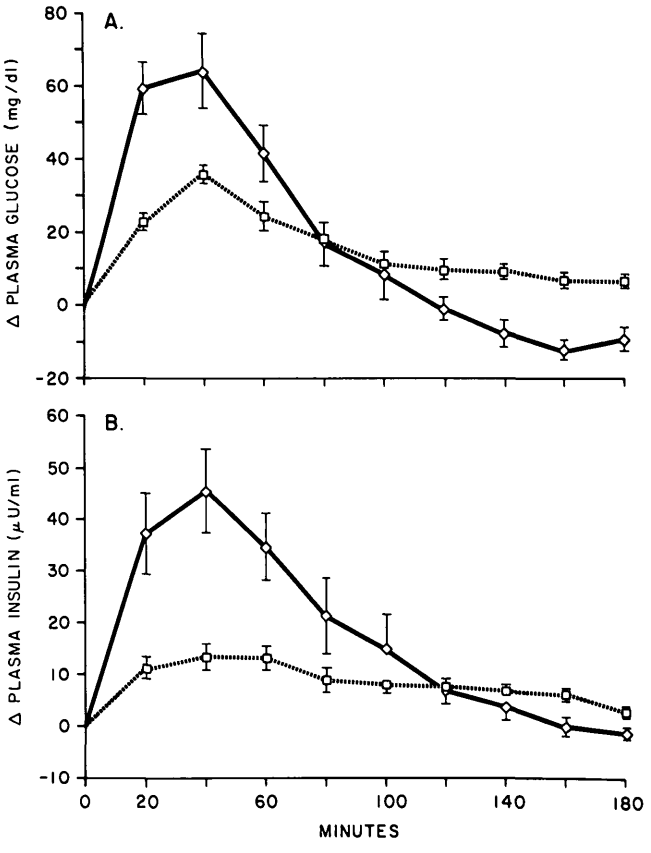

FIG. 2. Plasma glucose (*A*) and insulin (*B*) profiles for sucrose (◇, n = 12) or sucrose with guar (□, n = 16) ingested at breakfast at 0800; n = 12 for S meals, and n = 16 for S + G meals. Values represent means ± SE.

Plasma glucose and insulin profiles for S at breakfast (n = 12) versus S + G at breakfast (n = 16) were quite different (Fig. 2). When S was ingested for breakfast, the peak glycemic excursion occurred at 40 min, with plasma glucose rising 64.0 ± 10.2 mg/dl above baseline (Fig. 2*A*). Plasma glucose then fell, and after 120 min it was below baseline. Three hours after ingestion of S, the plasma glucose level was below the starting glucose concentration (76.1 ± 3.7 vs. 85.6 ± 2.7 mg/dl, $P < .01$). The plasma insulin profile (Fig. 2*B*) mimicked that of plasma glucose, with a prompt rise in plasma insulin levels in response to hyperglycemia (the maximal plasma insulin concentration was 53.1 ± 9.2 μU/ml at 40 min) followed by a rapid return to baseline by 160 min and a continued fall thereafter. The mean plasma insulin level 180 min after breakfast was slightly lower, al-

though not significantly so, than at 0 min (6.6 ± 0.9 vs. 7.8 ± 1.6 μU/ml, NS).

In contrast, when S + G was ingested at breakfast, plasma glucose again peaked at 40 min, but the glycemic excursion was less (35.8 ± 2.5 mg/dl), and the plasma glucose concentration never returned to baseline (Fig. 2*A*). Instead, mild hyperglycemia persisted, with the plasma glucose level 180 min after ingestion still being 6.5 ± 2.0 mg/dl above baseline (91.0 ± 2.3 vs. 84.5 ± 2.1 mg/dl, $P < .003$). Plasma insulin levels rose more gradually in response to the slowly absorbed meal (maximal plasma insulin concentration was 18.2 ± 2.7 μU/ml at 40 min) and then remained elevated during the persistent hyperglycemia (Fig. 2*B*). The mean plasma insulin level 180 min after ingestion of S + G was significantly higher than at 0 min (7.7 ± 1.0 vs. 4.9 ± 0.4 μU/ml, $P < .003$).

Effect of guar at breakfast on glucose and insulin profiles of subsequent meal. Figure 3*A* demonstrates that if S was ingested at breakfast at 0800, the $AUC_{glucose}$ for lunch at 1145 was similar to that for breakfast regardless of whether lunch consisted of S (protocol I) or S + G (protocol III). However, if S + G was ingested at breakfast, the $AUC_{glucose}$ for lunch at 1145 was 44 ± 12% of that for breakfast if lunch consisted of S + G ($P < .005$; protocol II) and 75 ± 30% if lunch consisted of S (protocol IV). None of the six subjects in protocol II and only one (subject 1) of the five subjects in protocol IV failed to exhibit a fall in $AUC_{glucose}$ for lunch. If data on subject 1 are excluded from analysis, the $AUC_{glucose}$ value for S of protocol IV at lunch was only 47 ± 13% of that for S + G at breakfast ($P < .03$, $n = 4$). In protocol V, when S + G was eaten for breakfast at 0800 and lunch consisting of S was delayed by 2 h, i.e., ingested at 1345, the $AUC_{glucose}$ values for the two meals were similar. It should be noted that in each protocol, plasma glucose concentrations before breakfast and before lunch were similar (data not shown).

Figure 3*B* depicts $AUC_{insulin}$ values. In protocols I–IV, no significant differences were noted between $AUC_{insulin}$ values for lunch and breakfast. However, in protocol V, when S was ingested at lunch 345 min after S + G for breakfast, $AUC_{insulin}$ for lunch was significantly greater than for breakfast ($P < .04$).

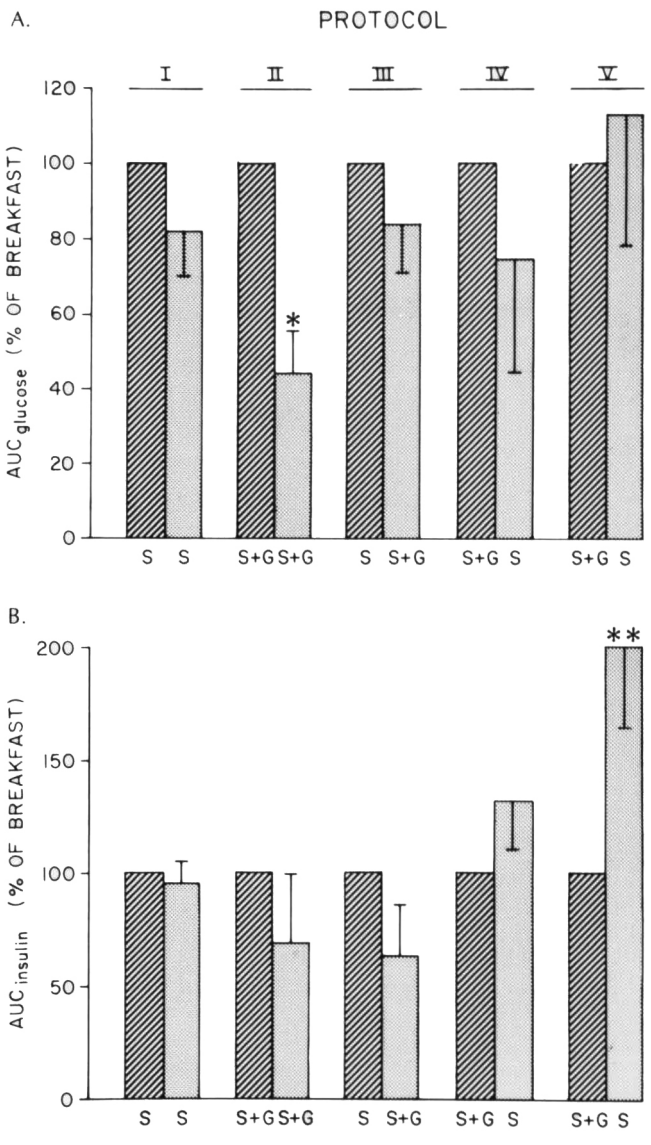

FIG. 3. Area under curve $(AUC)_{glucose}$ (*A*) and $AUC_{insulin}$ (*B*) for sucrose (S) and sucrose with guar (S + G) ingested at breakfast (*hatched bars*) (0800) or lunch (*shaded bars*). In protocols I–IV, lunch was eaten at 1145, whereas in protocol V, it was eaten at 1345; $n = 6$ for protocols I–III, and $n = 5$ for protocols IV and V. Data for each protocol have been normalized to breakfast value and are presented as means ± SE. *$P < .005$ compared with breakfast value of protocol II. **$P < .04$ when compared with breakfast value of protocol V.

DISCUSSION

The addition of guar to a sucrose challenge reduces the glycemic and insulin excursions of that carbohydrate by decreasing its rate of absorption. However, this attenuation of the glycemic excursion occurs at the expense of prolonged mild hyperglycemia. Although plasma glucose and insulin levels returned to baseline 120 and 160 min, respectively, after ingestion of S during breakfast, plasma glucose and insulin levels 180 min after ingestion of S + G at that time were still significantly above baseline. When $AUC_{glucose}$ was used as a measure of total glycemic excursion, no difference was observed between a breakfast challenge consisting of S versus one consisting of S + G, even though the possibility of demonstrating a difference was optimized by regarding all negative δ-glucose values as equivalent to zero for the purpose of calculating $AUC_{glucose}$. However, because of the limited number of observations, the possibility of type 2 error exists.

The $AUC_{insulin}$ for S + G at breakfast was significantly lower than for S and may demonstrate a beneficial effect of guar on meal insulin requirements. The mechanism

for this decrease in insulin need is unknown, but it may reflect a more constant and appropriate secretion pattern of insulin. With an S challenge, plasma glucose levels fell significantly below baseline, suggesting too exuberant a release of insulin.

Of greater import, however, is the observation that the addition of guar to a test carbohydrate markedly reduces the glycemic excursion of the subsequent carbohydrate challenge. Jenkins and colleagues (13,14) previously demonstrated that a lentil (slowly absorbed carbohydrate) breakfast improves the glucose tolerance of the lunch meal and that the addition of guar to a glucose drink decreases the glycemic excursion to glucose ingested 4 h later. The mechanisms for these effects, however, were not elucidated. In this study, we show that the addition of guar to sucrose *1*) prolongs absorption of sucrose, *2*) leads to persistent hyperglycemia of a mild degree, *3*) results in persistently elevated plasma glucose and insulin levels 180 min after ingestion, *4*) decreases the magnitude of plasma glucose and insulin excursions, and *5*) reduces $AUC_{glucose}$ of the subsequent meal. In addition, we demonstrate that by increasing the time interval between the breakfast and lunch challenges by 2 h (a total of 345 min), guar's beneficial effect on the glycemic excursion of the subsequent meal could be abolished.

Finally, note that $AUC_{insulin}$ for lunch (S) in protocol IV was not different from that for breakfast (S + G), whereas in protocol V, it was significantly greater. $AUC_{insulin}$ for S should be greater than for S + G (vide supra). Therefore, these observations suggest that *1*) the addition of guar to sucrose reduces $AUC_{insulin}$ of the subsequent meal, and *2*) by increasing the time interval between the breakfast and lunch challenges by 2 h, this effect could be abolished as well.

These observations suggest that the prolonged elevation of plasma insulin levels accompanying a meal mixed with guar is responsible for the improved glycemic excursion of the subsequent meal, perhaps by continuing to exert a biological effect or by enhancing the action of subsequently secreted insulin. Note that Kingston et al. (8) recently demonstrated in normal men a rapid enhancement of tissue sensitivity to insulin following an oral glucose challenge and attributed this to an action of insulin to increase tissue insulin sensitivity. Similarly, we believe it likely that the prolonged elevation in plasma insulin levels accompanying a slowly absorbed meal may enhance insulin sensitivity during the subsequent meal, despite the fact that the plasma insulin concentration may have returned to baseline by the start of the second meal. Note that plasma glucose levels before breakfast and before lunch were similar; therefore, improved second-meal carbohydrate tolerance was not due to differences in starting glucose concentrations.

It seems unlikely that the improved glucose tolerance observed for a lunch eaten subsequent to S + G for breakfast was merely an effect of guar given at breakfast on the absorption rate of lunch. Intimate mixing of guar with glucose before ingestion is required to delay absorption (15), and if guar was administered as little as 2 min before taking a glucose drink, no effect on glycemic excursion was observed (16). When total oral glucose absorption was assessed with a ^{14}C-labeled glucose tracer, the addition of 20 g guar to a breakfast of 50 g glucose decreased the absorption of a glucose lunch served 4 h later by <10% (17). Finally, it is interesting to note that the beneficial effect of guar on the glucose tolerance of a subsequent meal could be mimicked by continuous sipping of a guar-free glucose drink over 4 h (15). These observations, coupled with our own, strongly suggest that the prolonged absorption pattern of breakfast, rather than any residual effect of guar, was responsible for the improved glucose tolerance of the second meal.

Our findings are also consistent with those of Service et al. (18), who found no effect of time of meal ingestion on insulin requirements for identical mixed meals in a group of nonobese type I diabetic patients. They also observed that insulin requirements for a meal were significantly affected by the size of the preceding meal; i.e., as the size of the preceding meal increased, the insulin requirement for the subsequent meal decreased. One might reason that as the size of a meal increased, its absorption would be prolonged and the duration of hyperglycemia and elevated insulin levels would progressively increase. Therefore, it is possible that, not the size of the preceding meal, but rather the duration of its absorption, was the factor responsible for the decrease in the second meal's insulin requirements.

These observations indicate that the difference in insulin requirements between breakfast and subsequent meals is not due to morning insulin resistance and is not linked to the dawn phenomenon. Instead, it appears that more attention needs to be devoted to how absorption patterns of foodstuffs affect plasma insulin profiles. In addition, the effects of the temporal proximity of one meal to another and of meal absorption characteristics need to be taken into account when designing studies to examine the physiological profiles of various meals (e.g., when comparing meals based on the glycemic index with those based on food exchanges).

We have invoked the Staub-Traugott effect to explain our findings. This effect refers to the improved disposal of a second glucose load administered shortly after a primary glucose challenge. Our data present a corollary of this phenomenon, indicating that the spacing interval between the two challenges required to observe the effect can be prolonged if the initial load is absorbed slowly. With a rapidly absorbed carbohydrate load (S), the longest spacing interval permitting the effect to be observed was <3 h. With a slowly absorbed carbohydrate load (S + G), the longest interval was between 3.75 and 5.75 h. Although the mechanism of the Staub-Traugott effect is not known for certain, our findings, coupled with those of others, suggest that it may be related in some way to preceding hyperinsulinemia (8). It clearly is not related to enhanced β-cell responsiveness, because in our study and a previous study, insulin responses were less for the second carbohydrate challenge (7).

We can only speculate on the potential significance of this phenomenon in diabetic humans. This study suggests that in the diabetic patient who is on a regimen of preprandial insulin administration, either the absorption pattern of the rapid-acting preprandial insulin or the time interval between meals may affect the insulin requirement for the subsequent meal. In the type II (non-insulin-dependent) diabetic patient not taking exogenous insulin, the ingestion of a meal containing slowly absorbed carbohydrate (or, perhaps, even other insulin secretagogues such as protein) may result in mild and persistent endogenous insulin secretion, which may enhance the action of subsequently secreted insulin and decrease the insulin requirement for the subsequent meal. Therefore, by prolonging the absorption of meals, one might improve overall glucose tolerance and lessen insulin requirements of type II diabetic patients. We caution, however, that these possibilities, as well as the effect of incorporating protein and fat into the test meals, still need to be tested.

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