Glycemic responses in insulin-dependent diabetic patients: effect of food composition[1-3]

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ABSTRACT This study examined the hypothesis that the glucose component of food and not the total carbohydrate is the major determinant of the glycemic response in patients with insulin-dependent diabetes mellitus. Patients were given glucose alone, fructose alone, glucose + fructose, lactose, and glucose + fat + protein. Fructose given alone increased the blood glucose almost as much as a similar amount of glucose (78% of the glucose-alone area, $p < 0.05$). However, the same amount of fructose given with glucose produced no greater glycemic response than did glucose alone (108%). Similarly, galactose contributed only slightly to the glycemic response when given as lactose (122%, $p < 0.01$) whereas protein and fat had no additional glycemic effect (101%). To test the above hypothesis in natural foods, patients were fed an amount of bread (high glycemic index) or apple (low glycemic index) that contained 25 g glucose. Both challenges produced glycemic responses very similar to 25 g purified glucose. *Am J Clin Nutr* 1989;49:658–66.

KEY WORDS Glycemic index, insulin adjustment, glucose, fructose, galactose, protein, fat, insulin-dependent diabetes mellitus

Introduction

Insulin adjustment in a patient with insulin-dependent diabetes mellitus (IDDM) continues to be a very difficult and sometimes arbitrary maneuver (1). These patients have little endogenous insulin secretion and are therefore totally dependent on precise dosing of exogenous insulin to counterbalance the many factors that produce hyperglycemia and hypoglycemia. Food, of all the factors known to alter blood glucose, probably has the most frequent and usually a very dramatic impact on glucose control. Recently there has been a surge of interest in how food affects the blood glucose and particularly which food components contribute to an increase in the blood glucose.

Protein and fat seem to augment the glycemic response to food very little and in fact usually blunt the rate of increase in blood glucose by reducing the rate of absorption (2, 3). Therefore, carbohydrate appears to be the food component that produces almost all of the blood glucose increase after a meal. However, there is now substantial evidence that not all carbohydrates increase the blood glucose equally. Jenkins et al (4–6) presented evidence that the major reason for differences in the glycemic responses of food is a difference in food digestion and absorption. They coined the term glycemic index to describe these differences. Crapo et al (7, 8) and Vaaler et al (9) also showed that cooking has a significant influence on the glycemic responses of some foods, presumably by altering the digestibility of these foods. Gannon et al (10), on the other hand, suggested that the carbohydrate composition may be a more important determinant than the digestibility of the food. They showed that in patients with noninsulin-dependent diabetes mellitus (NIDDM), 50 g sucrose or lactose have less than one-half of the glycemic response of 50 g glucose. There were similar data reported in nondiabetics (11). However, these studies were hampered by considerable variations in insulin secretion after the different food challenges.

Therefore, we evaluated the following hypothesis in patients with IDDM: we propose that the differences in the glycemic responses of food are primarily determined by the amount of glucose in the food and only secondarily by the availability of that glucose. We propose that this is the case because nonglucose food components will not be converted to glucose when they are fed with glucose. In this study we sought to determine to what extent

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TABLE 1
Patient characteristics

Patient	Age	Percentage of IBW*	Race	Sex	Duration of IDDM†	Daily dose of ultralente
	y				*y*	*U*
1	25	104	W	M	14	26
2	23	111	W	M	7	32
3	24	115	W	F	14	28
4	26	99	W	M	7	44
5	36	91	B	M	13	46
6	42	109	W	M	19	12
7	30	106	W	F	17	36
8	45	92	W	F	34	22
9	27	99	W	F	2	22
10	37	111	W	M	19	44
11	58	103	W	F	36	16
12	32	108	W	M	9	80
$\bar{x}$	33.8	104			15.9	34

* Ideal body weight.
† Insulin-dependent diabetes mellitus.

nonglucose foods contribute to the glycemic response of food when they are eaten with glucose (either as a monosaccharide or a polymer). We chose patients with IDDM for two reasons. First, these are the patients who are most in need of precise information (as discussed above). Most studies reported previously were done in nondiabetic subjects or patients with NIDDM. Second, they have little endogenous insulin secretion, which could alter the glycemic response and, therefore, they should give the most reproducible results.

Methods

Subjects

Twelve patients with IDDM (**Table 1**) documented by a previous history of diabetic ketoacidosis were selected for these studies. All patients were on chronic therapy with 12–80 U ultralente insulin/d (Squibb, Princeton, NJ) to provide a stable blood glucose concentration before the food challenge and a constant basal insulin concentration during the challenge. These patients normally took regular insulin before each meal but this was not given during these studies. The mean age of these patients was 33.8 y with a mean duration of diabetes mellitus of 15.9 y. Patient 4 had peripheral neuropathy and patient 6 had autonomic neuropathy (impotence). Neither of these patients had evidence of significant delays in gastric emptying because their plasma glucose peaked within the first 2 h after glucose challenge, which was similar to the other patients. None of the patients had active retinopathy or proteinuria. All patients agreed to participate in this study under the provisions of the Institutional Review Board of the University of Alabama at Birmingham.

Experimental protocol

Patients were tested after 1000 to eliminate the effects of the dawn phenomenon. They were instructed to eat a small breakfast (and lunch if tested in the evening) and take a small premeal dose or doses of regular insulin. On arrival at the clinic (between 5 and 8 h after their last dose of regular insulin), an intravenous line was placed in a forearm vein for blood sampling and the patients were monitored until their blood glucose was stable (no change of > 1.0 mmol$\cdot$L$^{-1}\cdot$h^{-1}) between 3.33 and 8.33 mmol/L (mean pretest blood glucose concentration was 5.78 ± 0.44 mmol/L). A food challenge was administered by mouth and the blood glucose was measured every 10 min for the first 90 min and every 15 min for the next 90 min. All blood glucose measurements were made by use of a Glucoscan® meter and strips kindly donated by Lifescan Inc, Mountain View, CA. These measurements were checked hourly against either a meter of a different brand or an Autoanalyzer® (Beckman Instruments Inc, Fullerton, CA). Only one food challenge was given each day. The following challenges were given:

1) 25 g glucose alone (five β-D-glucose tablets with water).
2) 50 g glucose alone (five β-D-glucose tablets with water).
3) 25 g glucose (tablets) plus 24 g fructose (obtained in 3-g packs, powder mixed with water).
4) 24 g fructose alone.
5) 50 g lactose (providing 25 g glucose plus 25 g galactose, powder mixed with water).
6) 20 g glucose (tablets) plus a combination of 22.5 g protein and 30 g fat given as 7.5 slices of cotto salami (Oscar Meyer, Madison, WI). This quantity of salami contains 4 g glucose so that a total of 24 g glucose was given.
7) 55 g white bread containing 25 g glucose and 27 g total carbohydrate (from unpublished US Department of Agriculture [USDA] carbohydrate composition tables).
8) 543 g raw apple containing 25 g glucose and 52 g fructose (from unpublished USDA carbohydrate composition tables).

Initially, patients were given two glucose (alone, 25 g) challenges. The mean difference in the 3-h blood glucose area between these two challenges was 17.7% (range 1–40%). The patients were then given one or more of the other challenges. Again, each patient was given two challenges of each food. Not all patients were tested with all of the challenges but all were challenged with 25 g glucose alone.

Statistical analysis

All data are expressed as the mean ± SEM. The area under each blood glucose curve was determined by calculating the difference between the blood glucose at each time point and the blood glucose at time 0 and multiplying this value by the time interval (either 10 or 15 min) preceding this glucose determination. These time slices were then added together for the 3 h of each test. Because the data were found to be normally distributed by the Wilk-Shapiro test, either nonpaired or paired *t* tests were used to determine differences between groups. Two procedures for calculating the nonpaired *t* statistic were used to determine differences between blood glucose determinations at each time interval. First, all challenges were assumed to be independent tests and, therefore, the *n* that was used was the total number of tests performed. In the second analysis, the tests on each patient were averaged and the mean blood glucose was used; therefore, the n was the number of patients tested. Both analyses gave almost identical results except that occasionally the first analysis showed slightly higher statistical significance. Because we hypothesized that there would be no differences between the various food challenges and the first method of analysis is the one most likely to disprove this hypothesis, we elected to present the data analysed by this procedure. Similar analyses were done on the blood glucose area and peak blood

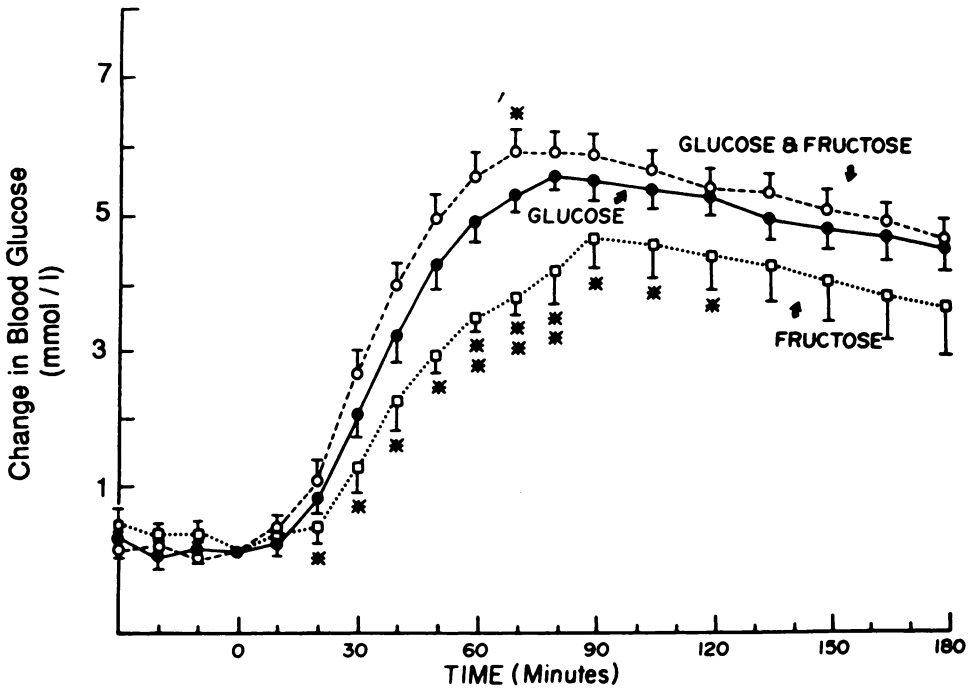

FIG 1. Change in blood glucose concentration ($\bar{x} \pm$ SEM) after 25 g glucose (●), 24 g fructose (□), and 25 g glucose plus 24 g fructose (○) in patients with insulin-dependent diabetes mellitus. The base-line blood glucose was 5.78 ± 0.28 mmol/L before the glucose challenge, 6.83 ± 0.44 mmol/L before the fructose challenge, and 6.17 ± 0.33 mmol/L before the glucose + fructose challenge. *$p < 0.05$ and **$p < 0.01$ by nonpaired t test compared with glucose alone.

glucose data. In addition, paired t test analyses were done on the blood glucose area data and power calculations were made based on $p < 0.05$, 80% power, and the assumption that a 30% difference in glycemic response is of clinical significance.

Individual glycemic indices were calculated for each patient for each food challenge in the following way: the mean 3-h glycemic response to a particular food challenge (eg, lactose) for each patient was divided by the mean 3-h glycemic response to glucose for that patient (100%) and multiplied by 100. Paired t tests were calculated using these values (12). This analysis makes it possible to determine whether some individuals respond differently than the group as a whole.

Results

To compare the glycemic responses of 50 and 25 g glucose, three patients were given glucose challenges of 50 and 25 g as glucose tablets (each challenge was given twice to each patient). Their responses to the two doses of glucose were compared. Their 3-h glucose areas were 1525 ± 48 vs 668 ± 30 mmol·L^{-1}·min^{-1} (50 g vs 25 g, $p < 0.001$) and their peak blood glucose response was 11.9 ± 0.3 vs 6.2 ± 0.4 mmol/L ($p < 0.001$). The mean individual glycemic index of 50 g glucose was 232% ± 6% (range 220%–239%). The peak blood glucose after 50 g glucose occurred between 60 and 105 min, similar to the majority of peak blood glucose responses after the 25-g glucose challenges. These data indicate that doubling the glucose load approximately doubles the 3-h glycemic response.

Next, five patients were challenged with 24 g fructose alone. **Figure 1** shows that the blood glucose was significantly lower after fructose than after a similar amount of glucose from 20 to 120 min (nonpaired t test). A similar result was obtained for the 3-h glucose area (**Fig 2,** fructose gives 78% of the glucose response, $p < 0.05$) and the peak blood glucose increase (**Fig 3,** fructose gives 75% of the glucose response, $p < 0.01$). However, when a paired t test was used for analysis, only the peak blood glucose was found to be significantly different at the $p < 0.05$ level. In addition, we found that the interindividual responses to fructose were extremely variable (ranging from 44% to 133%, 79% ± 16%) whereas the intraindividual responses were fairly consistent. Four patients had mean differences between their two tests similar to that seen with the glucose challenges (22%) whereas one patient had a 63% difference. From these tests, we concluded that a large amount of fructose when given by itself is rapidly absorbed and converted to glucose over a 3-h period. This process does not appear to convert 100% of the fructose to glucose in most cases, but usually converts over 50%. Therefore, fructose alone had a significant impact on the blood glucose in these patients.

We next tested the effect of fructose when given with a similar amount of glucose. Figure 1 shows that at only one time point was the glycemic response to glucose plus fructose greater than that of glucose alone. In addition, there was no difference in the 3-h blood glucose area (Fig 2) or the peak blood glucose response (Fig 3) when either paired or nonpaired t tests were used for analysis. Power calculations demonstrated that we had ample power to detect even a 15% difference in glycemic responses in

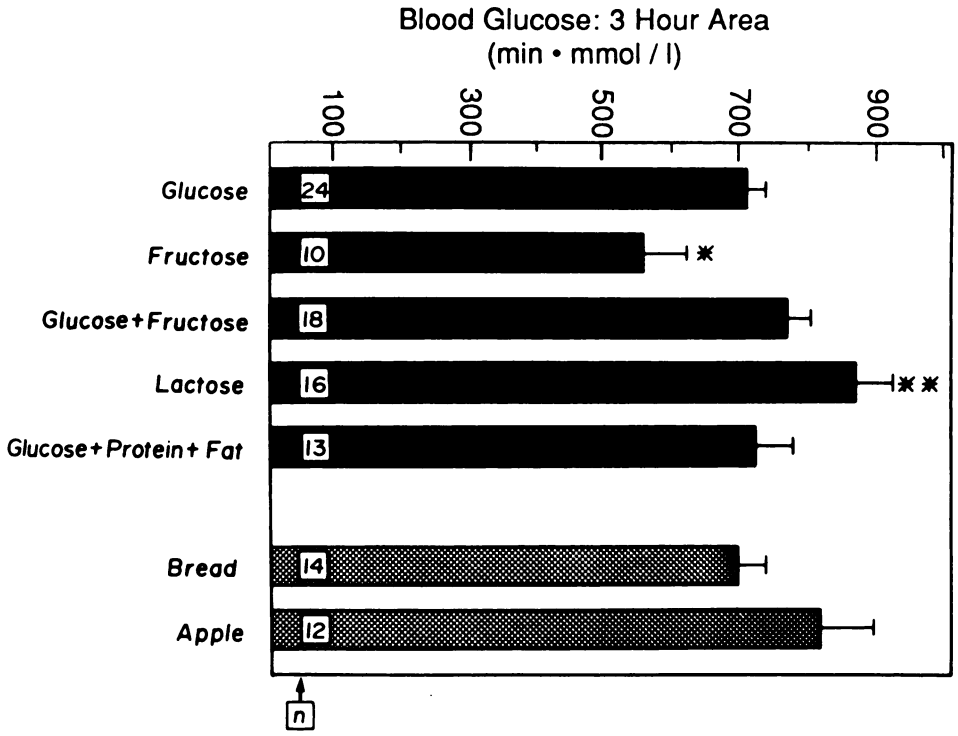

FIG 2. Three-hour blood glucose area (see methods for calculation procedure) after oral challenge of the indicated foods. The bread and apple each had an estimated glucose content of 25 g. The number of tests are shown in the box inside each bar. Each challenge was given twice to each patient. $\bar{x} \pm$ SEM, compared with glucose alone: $^{*}p < 0.05$ by nonpaired t test and NS by paired t test; $^{**}p < 0.01$ by nonpaired t test and $p < 0.05$ by paired t test.

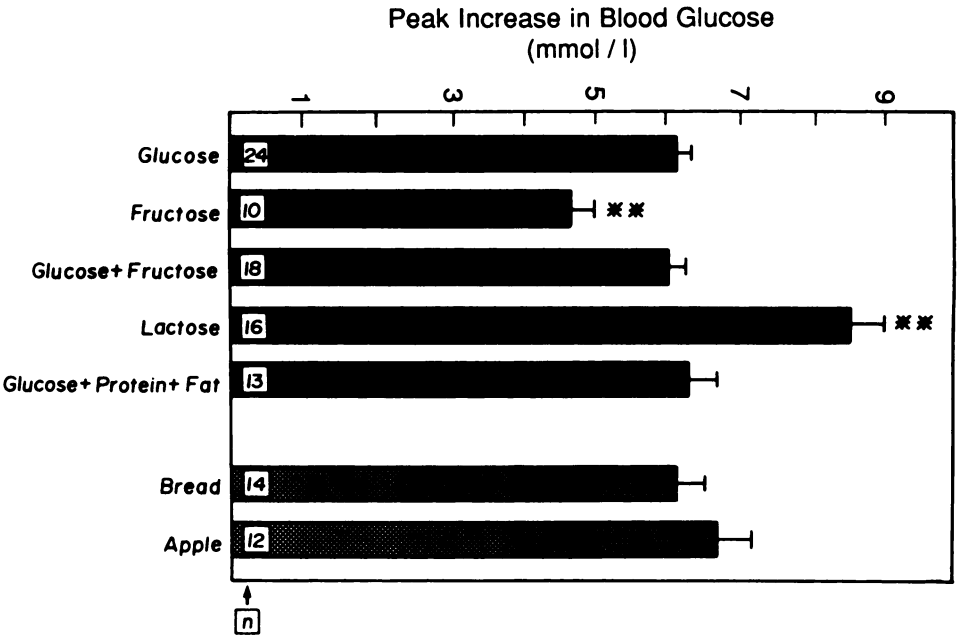

FIG 3. Maximum increase in blood glucose after oral challenge of the indicated foods. Format same as Figure 2. $^{**}p < 0.01$ by nonpaired t test and $p < 0.05$ by paired t test compared with glucose alone.

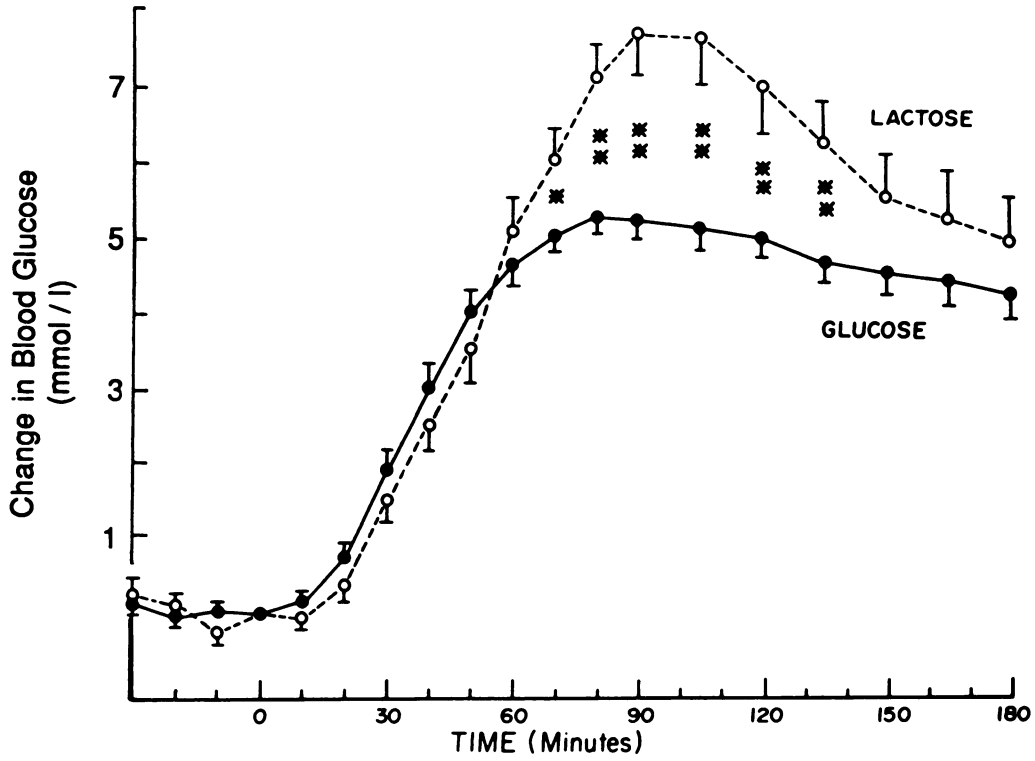

FIG 4. Change in blood glucose concentration ($\bar{x}$ ± SEM) after 25 g glucose (●) and 50 g lactose containing 25 g glucose plus 25 g galactose (○) in patients with insulin-dependent diabetes mellitus. The base-line blood glucose was 5.78 ± 0.28 mmol/L before the glucose challenge and 5.28 ± 0.33 mmol/L before the lactose challenge. *$p < 0.05$ and **$p < 0.01$ by nonpaired t test compared with glucose alone.

these patients (five patients would be required whereas we tested nine). This is because of the low individual variability in these tests compared with the fructose alone challenges. The individual glycemic indices support the lack of response to fructose in that the highest response that we saw in any single patient was 127% and the average response was 106% ± 11%. These results indicate that very little fructose is converted to glucose when glucose is given at the same time.

Figure 4 shows the blood glucose response to lactose (containing 25 g glucose and 25 g galactose) compared with 25 g glucose alone. These results indicate that galactose does add to the glycemic response of glucose, at least transiently. After 3 h there was no longer any difference in the blood glucose concentrations. Similar small increases in the glycemic response were detected when the blood glucose area (Figure 2, 122% of the glucose alone response, $p < 0.01$) or the peak blood glucose response (Figure 3, 135% of the glucose alone response, $p < 0.01$) was examined in a nonpaired analysis. When a paired t test analysis of the blood glucose areas was performed, a similar significant difference was obtained ($p < 0.0125$). However, it must be recognized that this is not an adequate level of significance if the Bonferroni correction is applied. Because we are doing six comparisons, a p value of 0.008 is required on any individual comparison to be sure that the difference is truly significant. The mean individual glycemic index for lactose was 120% ± 6% (range 101–155, $p < 0.01$). This response was still substantially less than would be expected if all of the galactose were converted to blood glucose. Therefore, we conclude that galactose when given with glucose probably does have a small, transient impact on the blood glucose in these patients.

Figure 5 shows the blood glucose response to 25 g glucose + 22.5 g protein + 30 g fat compared with glucose alone (25 g). There were no significant differences in the glycemic responses to these two challenges except for some slight delay in the glycemic response during the protein and fat challenge (NS) as would be expected from previous studies (2, 3). Similarly, there were no differences in the blood glucose areas or the peak blood glucose responses (Figs 2 and 3). The mean individual glycemic index for glucose, protein, and fat was 97 ± 15. There was a much wider variability of responses to this challenge than was seen with the two previous challenges, both interindividual (glycemic indices ranged from 59% to 175%) and intraindividual (differences between the two tests ranged from 9% to 59%, $\bar{x}$ = 27%). Most patients had lower glycemic responses, probably the result of delayed stomach emptying, whereas one patient had a high response after both fat and protein challenges (one was very high, 200%). This type of response was very unusual because the patient with the next high-

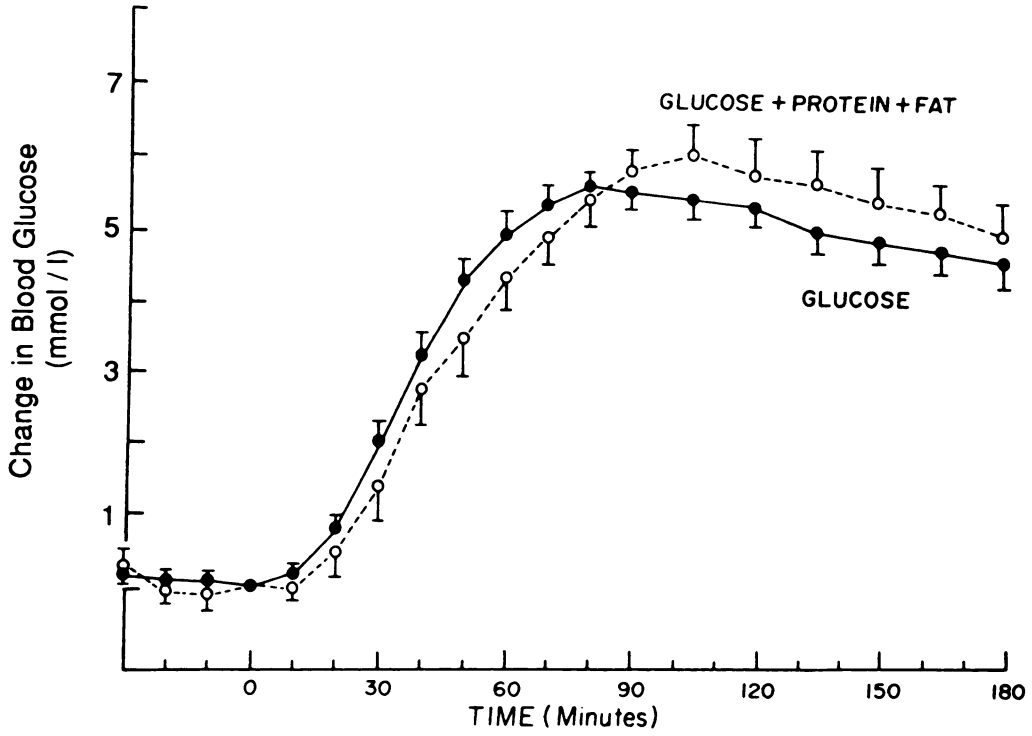

FIG 5. Change in blood glucose concentration ($\bar{x} \pm$ SEM) after 25 g glucose (●) and 24 g glucose plus 22.5 g protein plus 30 g fat (○) in patients with insulin-dependent diabetes mellitus. The base-line blood glucose was 5.78 ± 0.28 mmol/L before the glucose challenge and 5.94 ± 0.33 mmol/L before the protein plus fat challenge.

est response had an individual glycemic index of 114%. This patient appears to either convert substantial amounts of protein or fat to glucose or the protein or fat interferes with the utilization of the ingested glucose. Because of the substantial variability in this data, we do not have adequate power to detect a 30% difference (11 patients are required) in the glycemic responses. Therefore, we cannot say with confidence that there was no effect of protein and fat on the blood glucose even though we could not show a statistically significant difference.

To determine whether glucose and fructose from natural foods would behave in a fashion similar to that of purified sugars, we tested our patients with an amount of white bread (~92% of its carbohydrate is glucose) or apple (~30% of its carbohydrate is glucose) that contained 25 g glucose each. **Figure 6** shows that bread had a slightly slower glycemic response than did a similar amount of purified glucose whereas apple had a slightly higher response than would be expected from its estimated content of glucose (like lactose, this difference had disappeared 3 h after the challenge). However, there were no significant differences in either the blood glucose area or peak increase in blood glucose for either challenge when compared with 25 g purified glucose (Figs 2 and 3) by either nonpaired or paired *t* tests. In addition, we have adequate power with both challenges to detect a 30% difference in glycemic responses. The mean individual glycemic index for white bread was 101 ± 6% (range 82–130%, NS) and apple was 124 ± 11% (range 88–163%, $p < 0.05$). Note that the patient with the greatest response to apple also had the largest response to lactose (155%) and glucose + fructose (127%) but had a fairly small response to fructose alone (56%). It appears that there are some individuals that convert a small amount of fructose to glucose in this situation but the majority of fructose still does not contribute to the glycemic response of the food.

Discussion

There are two important features of our patient population. First, these were patients with IDDM; therefore, there was no endogenous insulin secretion to alter the glycemic responses of the food challenges. This greatly simplifies the interpretation of our data. It is likely that there was some residual regular insulin during these tests because they were started between 5 and 8 h after the previous insulin injection. However, this was unlikely to have had a significant impact because the patients blood glucoses were stable before the food challenge and the small amount of residual regular insulin is not likely to effect the large carbohydrate loads that were given (up to 75 g). Second, there are few published studies where patients with IDDM were used to determine glycemic responses to food. It is important to measure the glycemic responses of foods in those groups of patients in whom you wish to use the information (13).

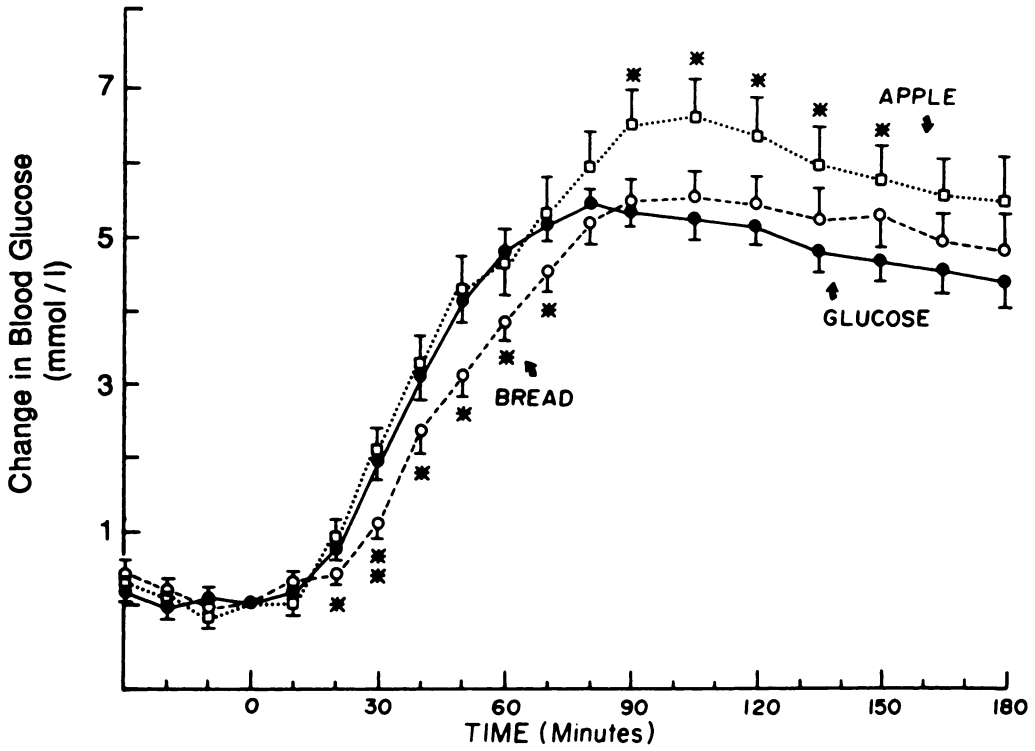

FIG 6. Change in blood glucose concentration ($\bar{x}$ ± SEM) after 25 g glucose (●), white bread containing 25 g glucose (○), apple containing 25 g glucose (□) in patients with insulin-dependent diabetes mellitus. The base-line blood glucose was 5.78 ± 0.28 mmol/L before the glucose challenge, 5.39 ± 0.33 mmol/L before the bread, and 5.39 ± 0.39 mmol/L before the apple. *$p < 0.05$ and **$p < 0.01$ by nonpaired t test compared with glucose alone.

Our studies in these patients with IDDM indicate that oral fructose given alone increased the blood glucose almost as much as a similar amount of glucose. However, the same amount of fructose given with glucose produced no greater glycemic response than glucose alone. Similarly, a mixture of protein and fat given with glucose rarely had any additional glycemic effect over that of glucose alone whereas galactose produced only ~20% of its expected glycemic response (if it were entirely converted to glucose) when given with glucose. From these results, we would conclude that the glucose content of the food is the major determinant of the glycemic response of that food. However, if a meal contains very little glucose (< 25 g) it is likely that other food components will be converted to glucose and increase the blood glucose concentration. We have no data as yet that indicates how much dietary glucose is required to prevent this conversion.

Falko et al (11) in nondiabetic individuals and Gannon et al (10) in patients with NIDDM reported results similar to ours. Of course their patients had significant endogenous insulin secretion that complicated their interpretations but despite this their results were very similar to the data that we report.

Jenkins et al (4–6) proposed that differences in the glycemic responses of different foods are due to differences in digestion and absorption. This is likely to be true in some foods, particularly those with a high fiber content and/or those that are uncooked (7–9) (foods in which the glucose is encapsulated in a poorly digestible matrix). It was clearly shown that these foods have very low glycemic responses. However, the bulk of food that is eaten by diabetic patients is (unfortunately) not uncooked or high in fiber so that these factors will play less of a role than the food composition. Note that Jenkin's high glycemic index foods tend to be starchy foods (starch is pure glucose) whereas many of his low glycemic index foods had a high content of fructose (fruits) or galactose (milk). Therefore, the relative glucose composition of these foods would predict the glycemic response if the nonglucose carbohydrates do not contribute to the glycemic response. We propose that the glucose content of a mixed meal will determine the maximum glycemic response but if some of the glucose is contained in poorly digestible foods, then this would lower the expected glycemic response. In addition, nonglucose carbohydrates will significantly increase blood glucose only if there is little glucose in the meal.

There is biochemical evidence that supports our hypothesis that ingested glucose prevents the conversion of amino acids and other simple sugars to glucose. These data were recently reviewed by Katz and McGarry (14). Because very little ingested glucose is taken up directly by the liver (15, 16), the peripheral blood glucose concentration should accurately reflect the amount of glucose ingested. Gluconeogenesis appears to continue for sev-

eral hours after food ingestion but the glucose-6-phosphate that is formed is diverted to glycogen synthesis rather than to free glucose (13, 16–19), apparently due to reduced activity of glucose-6-phosphatase by an unknown mechanism. Therefore, in the presence of dietary glucose, ingested fructose, galactose, or amino acids would become substrates for glycogen synthesis rather than for glucose production. An increase in the plasma insulin concentration could be expected to inhibit glucose production even further (16), suppressing even the little conversion to glucose that does occur (ie, with lactose above).

There have been studies in patients with IDDM that appear to conflict with our results. Bantle et al (20) demonstrated that potato and wheat starch produced the same glycemic response as glucose in patients with IDDM (as we would predict). However, sucrose produced almost the same response as glucose and the fructose response was only slightly less. The design of their study was such that all of the patients received 30 g starch and 12 g lactose in addition to the test carbohydrates. They presented no data to show the effect of this baseline meal alone but it will obviously contribute a significant amount to the total response because it provides 50% of the total carbohydrate. This would make it more difficult to identify differences between the various challenges. All of the challenges were given when the mean fasting plasma glucose was between 10 and 13.88 mmol/L. This could indicate that these patients were relatively insulin deficient at the time and probably had relatively uncontrolled gluconeogenesis. This would promote the conversion of fructose to glucose and further reduce the differences between the challenges. Finally, they gave very large challenges (84 g carbohydrate) and the peak plasma glucose concentrations were > 17.8 mmol/L. The mean urinary excretion of glucose during these challenges ranged from 21.5 to 27.7 g, which indicates that a large percentage of the carbohydrate was excreted in the urine. These factors would make it very difficult to identify differences even if they do exist. Their results in patients with NIDDM were actually very similar to ours. The wheat and potato produced increases essentially identical to glucose whereas sucrose produced a lesser increase and fructose produced the least increase. These patients all had fasting plasma glucose concentrations of < 10 mmol/L and their peak plasma glucose concentrations were all < 16.7 mmol/L (urinary glucose excretion < 6 g). These factors make the differences between the challenges more apparent.

Vaaler et al (21) reported that 36 g carbohydrate from apple (9 g glucose), banana (23 g glucose), and orange (19 g glucose) all produced the same glycemic response, which was very similar to 36 g glucose. In fact, the apple clearly had a larger response than the other fruits despite having less glucose. However, like the study by Bantle et al (20), these patients were all hyperglycemic before testing (10 mmol/L) and had peak blood glucose concentrations > 16.7 mmol/L.

If the Jenkin's food digestibility hypothesis is correct, then a tremendous amount of clinical information is needed to adjust meal insulin dosage. Every food of interest will need to be tested (6) in patients because all foods have unique structural properties that can influence their digestion. They will also have to be tested in a variety of combinations because different mixtures may alter digestion. If the carbohydrate composition theory is correct then the basic principles of food interaction can be utilized to estimate the expected glycemic response (eg, fructose will augment the blood glucose response very little in the presence of glucose). Efforts should then be directed to more thorough analysis of carbohydrate foods (accurate data is currently very scarce) so that this information would be available to patients. The major in vivo question then becomes: to what extent are other carbohydrates converted to glucose in a variety of clinical situations. Our studies with bread and apple indicate that very little conversion of fructose to glucose occurs in patients fed a moderate amount of glucose without insulin. However, more studies are required to determine the relative contributions of food composition and digestibility in other clinical situations with other food challenges. These studies should be done in patients with IDDM because these are the patients who are most likely to use the information.

These questions become critical in these times of very tight blood glucose control because patients are commonly maintaining blood glucose concentrations in the normal range and even mild excesses of insulin can cause significant hypoglycemic reactions. If patients take insulin based on the total carbohydrate content of meals and the fructose or galactose does not increase their blood glucose but they take insulin as if it will, then they are in danger of having a hypoglycemic reaction. For example, if our patients had taken three times as much insulin for their apple meal as they took for their bread meal (because it contained three times as much carbohydrate), it is very likely that they would have had severe insulin reactions after the apple because their blood glucose responses were so similar. Of course, it is even more dangerous if they are only using calories to determine their meal size because the bulk of calories (fat and protein) probably produce very little increase in the glycemic response of the food and probably delay absorption, which increases the risk of hypoglycemia.

In conclusion, we presented evidence that a major determinant of the glycemic responses of patients with IDDM is the glucose content of food. If this hypothesis is confirmed with additional studies of mixed meals with a known content of glucose, then we would propose that the premeal dosing of insulin in these patients should be adjusted primarily according to the glucose content of the food and secondarily on the available glucose.

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