

Different glycemic indexes of breakfast cereals are not due to glucose entry into blood but to glucose removal by tissue¹⁻³

Simon Schenk, Christopher J Davidson, Theodore W Zderic, Lauri O Byerley, and Edward F Coyle

ABSTRACT

Background: The glycemic index (GI) of a food is thought to directly reflect the rate of digestion and entry of glucose into the systemic circulation. The blood glucose concentration, however, represents a balance of both the entry and the removal of glucose into and from the blood, respectively. Such direct quantification of the postprandial glucose curve with respect to interpreting the GI is lacking in the literature.

Objective: We compared the plasma glucose kinetics of low- and high-GI breakfast cereals.

Design: On 2 occasions, plasma insulin concentrations and plasma glucose kinetics (by constant-rate infusion of [6,6-²H₂]glucose) were measured in 6 healthy males for 180 min after they fasted overnight and then consumed an amount of corn flakes (CF) or bran cereal (BC) containing 50 g available carbohydrate.

Results: The GI of CF was more than twice that of BC (131.5 ± 33.0 compared with 54.5 ± 7.2 ; $P < 0.05$), despite no significant differences in the rate of appearance of glucose into the plasma during the 180-min period. Postprandial hyperinsulinemia occurred earlier with BC than with CF, resulting in a 76% higher plasma insulin concentration at 20 min (20.4 ± 4.5 compared with 11.6 ± 2.1 $\mu\text{U/mL}$; $P < 0.05$). This was associated with a 31% higher rate of disappearance of glucose with BC than with CF during the 30–60-min period (28.7 ± 3.1 compared with 21.9 ± 3.1 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; $P < 0.05$).

Conclusion: The lower GI of BC than of CF was not due to a lower rate of appearance of glucose but instead to an earlier postprandial hyperinsulinemia and an earlier increase in the rate of disappearance of glucose, which attenuated the increase in the plasma glucose concentration. *Am J Clin Nutr* 2003;78(suppl):742–8.

KEY WORDS Carbohydrate, glucose kinetics, protein, nutrition, hyperinsulinemia

INTRODUCTION

More than 20 y ago, the concept of the glycemic index (GI) was introduced as a means of physiologically classifying carbohydrate-containing food (1). Briefly, the GI compares the postprandial increase in the plasma glucose concentration (ie, the glycemic response) from a fixed amount of available carbohydrate in a test food with the glycemic response elicited from the same amount of carbohydrate in a standardized reference food (eg, glucose or white bread) (1, 2). By comparing the area under the postprandial plasma glucose curve of the test food with that of the reference food, which is given a relative value of 100, foods receive a numeric value and are then generally classified as having a high, moderate, or low GI (3).

A fundamental assumption regarding low-GI foods is that they produce a low glycemic response as a result of a slower rate of digestion of carbohydrate in the intestinal lumen, and that this subsequently slows the absorption of glucose into the circulation (1, 2, 4–7). The plasma glucose concentration, however, is a function of both the rate of appearance of glucose ($R_{a_{\text{glucose}}}$) into the systemic circulation and the rate of disappearance of glucose ($R_{d_{\text{glucose}}}$) from the systemic circulation. Some properties of foods that may influence $R_{a_{\text{glucose}}}$ (ie, glucose absorption from the intestines into the portal and peripheral circulation) include the intrinsic properties of the carbohydrate (eg, gelatinization and amylose-to-amylopectin ratio) and the fiber and fat contents of the food (8–10). The $R_{d_{\text{glucose}}}$ (ie, glucose uptake from the blood by tissue) is primarily influenced by insulin secretion and action on tissue (11). Although glucose is the primary macronutrient that stimulates insulin release, protein may augment insulin release when ingested with carbohydrate (12–14).

The rate at which the carbohydrate in a food is absorbed into the blood as glucose can only be inferred by directly measuring the plasma glucose kinetics (ie, $R_{a_{\text{glucose}}}$) and not from the GI. For example, a food can have a low GI as the result of having either a relatively low $R_{a_{\text{glucose}}}$ or a relatively high $R_{d_{\text{glucose}}}$. To our knowledge, no studies comparing the GI of foods have actually measured plasma glucose kinetics. Thus, direct data regarding the underlying factors responsible for differences in the GI of foods seem absent from the literature. Therefore, the purpose of the present study was to describe the underlying glucose kinetics responsible for the different glycemic responses of popular low- and high-GI breakfast cereals (2).

SUBJECTS AND METHODS

Subjects

Six healthy male subjects were recruited from the local community to participate in this study. The mean (\pm SEM) age,

¹ From the Human Performance Laboratory, Department of Kinesiology and Health Education, The University of Texas at Austin (SS, CJD, TWZ, and EFC), and the Stable Isotope Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA (LOB).

² Supported in part by the Quaker Oats Company.

³ Address reprint requests to EF Coyle, Department of Kinesiology and Health Education, The University of Texas at Austin, Bellmont Hall 222, Austin, TX 78712. E-mail: coyle@mail.utexas.edu.

Received January 27, 2003.

Accepted for publication April 23, 2003.

TABLE 1Macronutrient composition of the breakfast cereals with a low (bran cereal) or high (corn flakes) glycemic index¹

	Serving size	Total CHO	Available CHO ²	Fiber			Protein	Fat	Energy
				Total	Soluble	Insoluble			
	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>kJ</i>
Bran cereal	119.2	88.5	50.0	38.5	3.0	35.5	15.4	3.8	1238
Corn flakes	60.9	51.7	50.0	1.7	1.4	0.3	4.3	0	909

¹50 g available carbohydrate was provided in both trials; *n* = 6. CHO, carbohydrate. Bran cereal was All-Bran Original (Kellogg's, Battle Creek, MI); corn flakes were Kellogg's Corn Flakes.

²Available CHO = total CHO – total fiber.

weight, height, and body mass index (in kg/m²) of the subjects were 27.8 ± 1.5 y, 74.8 ± 3.3 kg, 180.8 ± 3.0 cm, and 22.8 ± 0.24, respectively. The subjects had normal glucose tolerance as evaluated by use of an oral-glucose-tolerance test. The subjects were informed of the experimental protocol and the possible risks involved before signing a consent form approved by The University of Texas at Austin Internal Review Board.

Diet and exercise control

The day before the initial trial, the subjects were instructed to record their diet and then to repeat this diet the day before subsequent trials. Notably, the final meal of the day was a standardized snack of high glycemic carbohydrate (0.5 g/kg). This was provided to ensure that the initial plasma substrate concentrations and any measured metabolic differences between the trials were not a consequence of the final meal (15). Physical activity was standardized the day before all experimental trials, with subjects undertaking cycling exercise for 1 h at ≈60% of their age-predicted maximum heart rate.

Experimental meals

The experimental cereals were a bran cereal (BC; All-Bran Original; Kellogg's, Battle Creek, MI) and a corn flakes cereal (CF; Kellogg's Corn Flakes). These cereals were chosen because they are popular breakfast cereals and were previously shown to have a low (BC) and high (CF) GI (16). A placebo drink (flavored water) was used as the fasting control. In another trial, a glucose-water solution (GL) was given as the reference food so that the GI could be calculated for the cereals. Four hundred milliliters water was consumed with the meal during each trial. Each experimental meal (except the placebo drink) provided 50 g available carbohydrate. This amount was chosen according to the standardized protocol for determination of the GI as outlined by Wolever et al (2). The macronutrient composition of each meal is provided in **Table 1**.

Experimental protocol

On separate days and in random order, the subjects arrived at the laboratory in a fasted state (≈10 h); on arrival, catheters were inserted into a forearm vein of each arm for blood sampling and isotope infusion, respectively. A primed, constant-rate infusion of [6,6-²H₂]glucose (prime = 35 μmol/kg, constant infusion = 0.40 μmol · kg⁻¹ · min⁻¹; Isotec Inc, Miamisburg, OH) administered by using calibrated syringe pumps (Harvard Apparatus, South Natick, MA) was then initiated and maintained for 1.5 h before and for 3 h after ingestion of the experimental meal. There was no isotope infusion or measurement of plasma glucose kinetics during the GL meal, because this trial served only as the

reference for calculation of the GI of the cereals. During the 180 min after meal ingestion, the subjects remained seated in a standardized position and performed significant bodily movement only at 31, 91, and 151 min postprandially. At these times, they were allowed to urinate if necessary and were then asked to cycle a stationary ergometer for ≈3 s, performed 4 times with 2 min of seated recovery. This was part of another study and it was directly determined that this brief exercise did not alter plasma glucose kinetics (the CF trial was performed both with and without the exercise bouts; data not shown).

Blood sampling and analysis

Blood was sampled (6 mL) before the isotopic infusion began, immediately before ingestion of the experimental meal (0 min), and 20, 30, 60, 90, 120, 150, and 180 min postprandially for determination of plasma glucose and insulin concentrations and plasma glucose kinetics. Blood samples (4 mL) were also taken 54, 84, 114, 144, and 174 min postprandially for analysis of the plasma glucose concentration and plasma glucose kinetics only. During the GL meal, blood was sampled (6 mL) only at 0, 20, 30, 60, 90, 120, 150, and 180 min for analysis of plasma glucose and insulin concentrations. Four milliliters from each sample was placed into prechilled tubes containing 0.2 mL EDTA solution (25 mg/mL) for determination of plasma glucose concentrations and plasma glucose kinetics. Blood (2 mL) for plasma insulin analysis was placed into prechilled tubes containing 0.2 mL EDTA (25 mg/mL) and aprotinin (0.5 U/mL). Plasma was separated by centrifugation (3 × *g* for 20 min at 4 °C), transferred to 12 × 75 mm plastic tubes, and immediately frozen at –80 °C for subsequent analysis. Plasma glucose concentrations were measured by use of a Colorimetric assay (Trinder; Sigma Inc, St Louis), and plasma insulin concentrations were measured by radioimmunoassay (Linco Research, Inc, St Charles, MO).

Isotope enrichment sample preparation

Plasma samples (300 μL) were deproteinized with 450 μL 0.3 N Ba(OH)₂ and 450 μL 0.3 N ZnSO₄, mixed by vortexing, and incubated in an ice bath for 20 min. After centrifugation at 3 × *g* for 15 min at 4 °C, the supernatant fluid was passed down an ion-exchange column and was then rinsed 5 times with 400 μL distilled water. The samples were captured in 13 × 75 mm glass screw-cap tubes and dried overnight by using compressed air. Acetic anhydride (75 μL) and pyridine (75 μL) were added to the dried samples, which were then incubated at 100 °C for 1 h and subsequently dried with nitrogen gas. The samples were then resuspended in ethyl acetate and injected into a gas chromatograph–mass spectrometer with an autosampler (5890 Series II 5988a mass

spectrometer; Hewlett-Packard, Palo Alto, CA), and the 200 and 202 masses of the pentaacetate derivative of glucose were monitored with selective ion monitoring.

Calculations

The area under the curve (AUC) for glucose and insulin was obtained by calculating the AUC over the 180-min postprandial period by using the trapezoidal method. Only values above fasting concentrations were included. The GI was calculated by dividing the respective glucose AUC for BC and CF by the glucose AUC for GL and multiplying by 100. Glucose kinetics (ie, Ra_{glucose} and Rd_{glucose}) were calculated by using the one-pool, non-steady state equations of Steele (17), modified for use with stable isotopes:

$$Ra_{\text{glucose}} = \{F - V_d \times [(C_1 + C_2)/2] \times [(E_2 - E_1)/(t_2 - t_1)]\} / [(E_2 + E_1)/2] \quad (1)$$

$$Rd_{\text{glucose}} = Ra_{\text{glucose}} - \{V_d \times [(C_2 - C_1)/(t_2 - t_1)]\} \quad (2)$$

$$GCR = Rd_{\text{glucose}} / [(C_2 + C_1)/2] \quad (3)$$

where F is the isotope infusion rate, V_d is the effective volume of distribution, C is the plasma concentration of the tracee, $(E_2 - E_1)/(t_2 - t_1)$ is the change in enrichment (ie, E = tracer-to-tracee ratio) between 2 consecutive samples ($t_2 - t_1 = x$ min), and GCR is the glucose clearance rate. V_d was estimated to be 150 mL/kg (18).

Glucose kinetics were calculated for the following time periods: 0–20 min, 20–30 min, 30–54 min, 54–60 min, 60–84 min, 84–90 min, 90–114 min, 114–120 min, 120–144 min, 144–150 min, 150–174 min, and 174–180 min. Total Ra_{glucose} and Rd_{glucose} in μmol were subsequently calculated for each time period, and then the average glucose kinetics over a 30-min time period were calculated by dividing the total Ra_{glucose} or Rd_{glucose} by 30 min (ie, 0–30 min, 30–60 min, 60–90 min, 90–120 min, 120–150 min, and 150–180 min). The GCR represents an index of the glucose uptake relative to the prevailing plasma glucose concentration and thus gives an index of insulin-mediated plasma glucose uptake.

Experimental design and statistics

A two-way repeated-measures analysis of variance (ANOVA; cereal \times time) was used to determine significant main effects and interactions. When there was a significant interaction or main effect of time, mean contrasts according to modified Bonferroni inequalities were used to analyze dependent variables (plasma glucose and insulin concentrations, Ra_{glucose} , Rd_{glucose} , and GCR) at specific time points. A one-way repeated-measures ANOVA was used to analyze the GI and overall glucose AUC (ie, 180-min postprandial period). Data for the placebo mean are not presented because, as expected, plasma glucose and insulin values did not differ significantly from 0 min, ie, before meal ingestion. Statistical significance was defined as $P < 0.05$. All results are presented as means \pm SEMs.

RESULTS

Plasma glucose concentration, glucose area under the curve, and glycemic index

The postprandial plasma glucose concentration was significantly lower for BC than for CF at 54, 60, 84, and 90 min (all $P < 0.05$; Figure 1A). As a result, the glucose AUC for BC was significantly

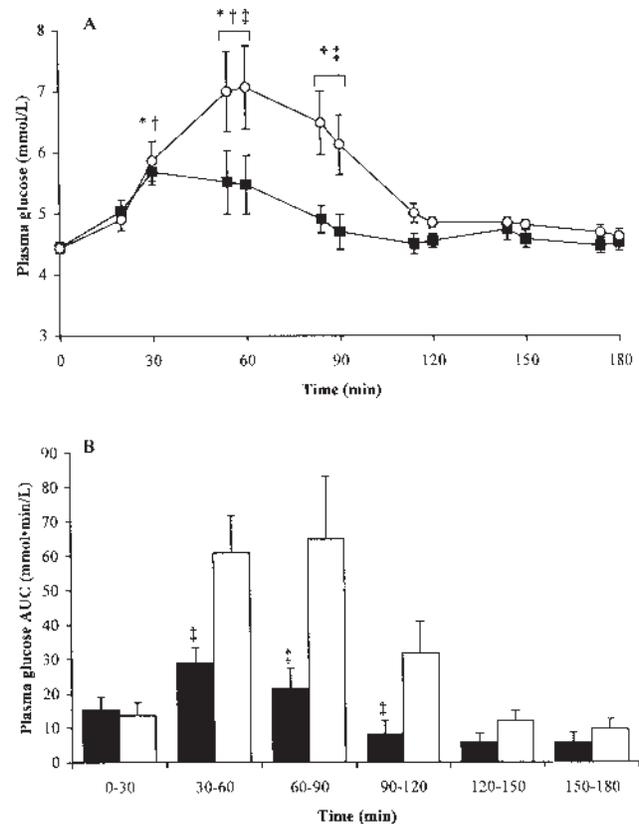


FIGURE 1. Mean (\pm SEM) plasma glucose concentration (A) and incremental 30-min plasma glucose response [area under the curve (AUC)] (B) for 180 min after subjects ($n = 6$) ingested a breakfast cereal with a low [bran cereal (BC); ■] or high [corn flakes (CF); ○ and □] glycemic index. Each cereal provided 50 g available carbohydrate. Two-way ANOVA showed a main effect of time and a significant cereal-by-time interaction (both $P < 0.05$). Mean contrasts according to modified Bonferroni inequalities were used to analyze significance at specific time points ($P < 0.05$). *BC significantly different from time 0. †CF significantly different from time 0. ‡BC significantly different from CF.

lower than that for CF from 30 to 120 min (all $P < 0.05$; Figure 1B). Moreover, the glucose AUC for the 180-min postprandial period (192.5 ± 38.4 compared with 85.7 ± 12.1 mmol \cdot min/L; $P < 0.05$) and the GI (131.5 ± 33.0 compared with 54.5 ± 7.2 ; $P < 0.05$) for CF were more than twice those for BC.

Plasma rate of appearance of glucose

There was no cereal-by-time interaction for CF and BC during the 180-min postprandial period, indicating that the change in Ra_{glucose} was not significantly different between CF and BC (Figure 2). There was a main effect of time for both BC and CF, whereby Ra_{glucose} significantly increased above the fasted state during the initial 120 min after meal ingestion ($P < 0.05$).

Plasma insulin concentration and insulin area under the curve

The plasma insulin concentration 20 min postprandially was $>75\%$ higher for BC than for CF (20.4 ± 4.5 compared with 11.6 ± 2.1 $\mu\text{U}/\text{mL}$; $P < 0.05$; Figure 3A). In light of this, the insulin AUC was more than twice as great for BC during the 0–30-min postprandial period (288.7 ± 71.0 compared with $128.4 \pm$

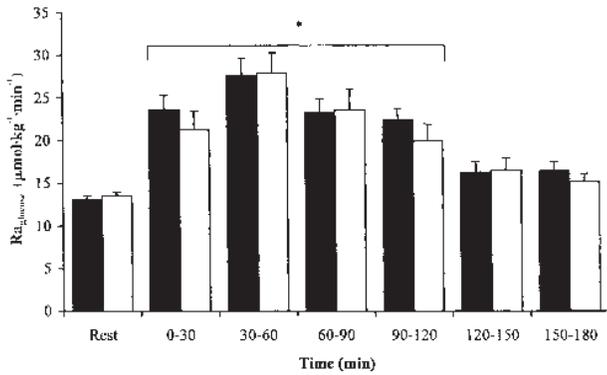


FIGURE 2. Mean (\pm SEM) rate of plasma glucose appearance (Ra_{glucose}) at rest and every 30 min for 180 min after subjects ($n = 6$) ingested a breakfast cereal with a low [bran cereal (BC); ■] or high [corn flakes (CF); □] glycemic index. Each cereal provided 50 g available carbohydrate. Two-way ANOVA showed a main effect of time ($P < 0.05$), but showed no cereal-by-time interaction. Given that there was no interaction but a main effect of time, mean contrasts according to modified Bonferroni inequalities were used only to analyze whether values for a given trial were significantly different from rest ($P < 0.05$). *Significantly different from rest, $P < 0.05$.

42.9 $\mu\text{U} \cdot \text{min}/\text{mL}$; $P < 0.05$; Figure 3B). The augmented postprandial hyperinsulinemia for BC was only transient, however, because there was no significant difference between the cereals at 30 min (25.5 ± 3.5 compared with 22.1 ± 4.6 $\mu\text{U}/\text{mL}$ for BC compared with CF; NS) or at any time point thereafter. Similarly, there were no further differences in the insulin AUC during the 30–180-min postprandial period nor any significant difference in the overall insulin AUC (1523.3 ± 155.7 compared with 1602.4 ± 138.9 $\mu\text{U} \cdot \text{min}/\text{mL}$ for BC compared with CF; NS).

Plasma rate of glucose disappearance and glucose clearance rate

The only significant difference in Rd_{glucose} between the cereals was during the 30–60-min postprandial period, whereby Rd_{glucose} was 31% higher for BC than for CF (28.7 ± 3.1 compared with 21.9 ± 3.1 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; $P < 0.05$; Figure 4A). Rd_{glucose} was not significantly different during the initial 0–30-min postprandial period (17.5 ± 1.5 compared with 14.1 ± 0.9 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for BC compared with CF) or during the 60–180-min period (all NS). Similar to Rd_{glucose} , the GCR was only significantly different between the cereals during the 30–60-min period, with the GCR for BC being 54% higher than that for CF (5.3 ± 0.8 compared with 3.5 ± 0.6 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; $P < 0.05$, Figure 4B). Furthermore, the GCR increased above the fasted state during the 30–60-min postprandial period for BC only and was delayed until 60–90 min for CF ($P < 0.05$). The increase in the GCR during the 30–60-min period was significantly correlated with the initial plasma insulin response as measured by the 0–30-min insulin AUC ($r = 0.71$, $P < 0.009$).

DISCUSSION

The purpose of the present study was to describe the underlying glucose kinetics responsible for the different glycemic responses of breakfast cereals with a low (BC) or high (CF) GI. The major finding of this study was that the more than 2-fold

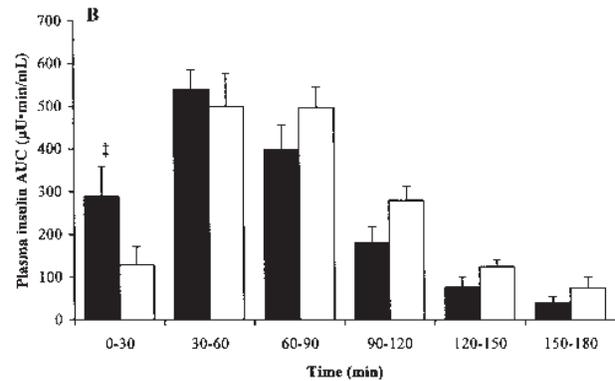
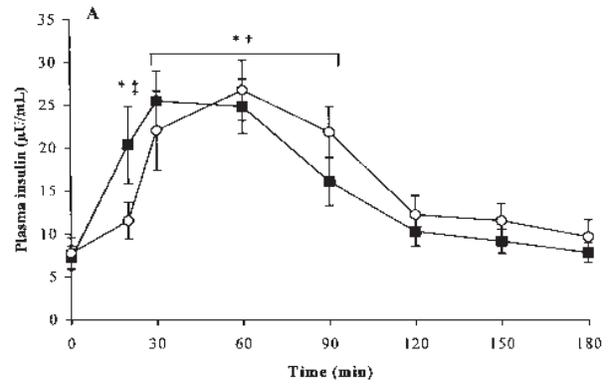


FIGURE 3. Mean (\pm SEM) plasma insulin concentration (A) and incremental 30-min plasma insulin response [area under the curve (AUC)] (B) for 180 min after subjects ($n = 6$) ingested a breakfast cereal with a low [bran cereal (BC); ■] or high [corn flakes (CF); ○ and □] glycemic index. Each cereal provided 50 g available carbohydrate. Two-way ANOVA showed a main effect of time and a significant cereal-by-time interaction (both $P < 0.05$). Mean contrasts according to modified Bonferroni inequalities were used to analyze significance at specific time points ($P < 0.05$). *BC significantly different from time 0. †CF significantly different from time 0. ‡BC significantly different from CF.

higher GI of CF than of BC (ie, 132 compared with 55) was not due to differences in Ra_{glucose} . Instead, BC showed a lower GI than did CF as a result of an earlier increase in Rd_{glucose} in association with an earlier and marked insulin response during the initial 20-min postprandial period. Simply, BC has a low GI because a more rapid insulin-mediated increase in tissue glucose uptake attenuates the increase in blood glucose concentration, despite a similar rate of glucose entry into the blood.

The fundamental assumption of the GI concept is that low-GI foods produce a lesser increase in the plasma glucose concentration as a result of slower rates of gastric emptying and digestion of carbohydrate in the intestinal lumen and, subsequently, a slower rate of absorption of glucose (ie, Ra_{glucose}) into the portal and systemic circulation (1, 2, 4–7). In the present study, we used stable-isotope methods to directly determine that although the GI of CF was more than 2-fold higher than that of BC, the postprandial change in Ra_{glucose} was not significantly different between CF and BC. It is perhaps surprising that despite the high fiber content of BC compared with CF (38.5 compared with 2.2 g), the Ra_{glucose} of BC was not significantly different from that of CF. However, BC

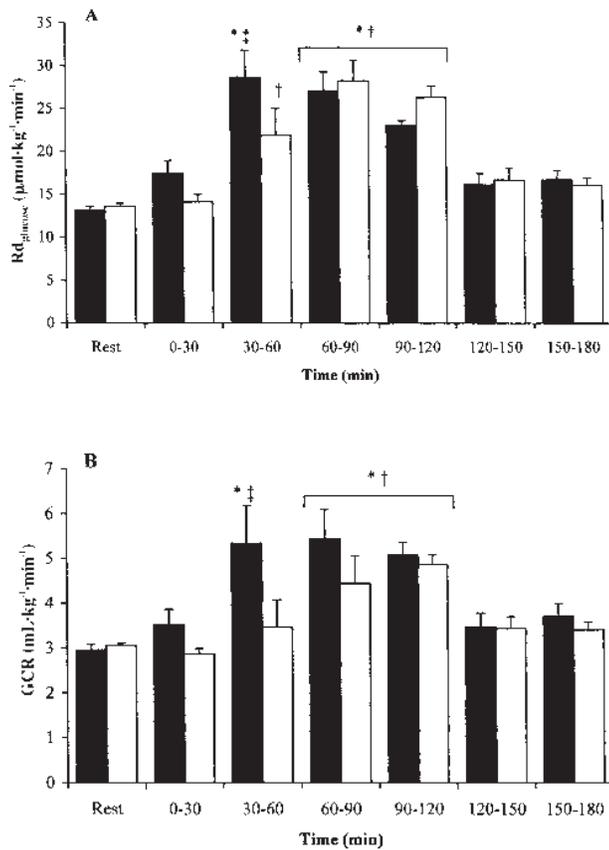


FIGURE 4. Mean (\pm SEM) rate of plasma glucose disappearance (Rd_{glucose}) (A) and the plasma glucose clearance rate (GCR) (B) at rest and every 30 min for 180 min after subjects ($n = 6$) ingested a breakfast cereal with a low [bran cereal (BC); ■] or high [corn flakes (CF); □] glycemic index. Each cereal contained 50 g available carbohydrate. Two-way ANOVA showed a main effect of time and a significant cereal-by-time interaction (both $P < 0.05$). Mean contrasts according to modified Bonferroni inequalities were used to analyze significance at specific time points ($P < 0.05$). *BC significantly different from rest, $P < 0.05$. †CF significantly different from rest, $P < 0.05$. ‡BC significantly different from CF, $P < 0.05$.

is composed primarily of insoluble wheat bran fiber ($\approx 92\%$), which has been shown to have little effect on reducing Ra_{glucose} when co-ingested with carbohydrate (19, 20). Also, BC contains a higher proportion of simple sugars than does CF (≈ 23 compared with ≈ 4 g), and this could be another reason that the Ra_{glucose} of BC was not significantly different from that of CF.

It is important, however, to bear in mind that although CF contains a small quantity of simple sugars, it still has a comparable Ra_{glucose} to BC. This observation is supported by the fact that although a food may be high in complex carbohydrate (eg, corn starch), this does not necessarily mean that the glycemic response will be low (21, 22). Differences in the gastric emptying rate could influence Ra_{glucose} , although given the fact that Ra_{glucose} was not significantly different between CF and BC, it is reasonable to hypothesize that the rate of available carbohydrate movement from the stomach into the intestines was similar. Independent of those factors that may influence Ra_{glucose} , it is noteworthy that we directly determined that the postprandial change in Ra_{glucose} was not significantly different between CF and BC.

Accordingly, the present study highlights that the GI is not solely a function of Ra_{glucose} .

An increase in the plasma glucose concentration above postabsorptive concentrations is the primary stimulus for increased insulin secretion. Given that Ra_{glucose} was not significantly different between trials, the change in plasma insulin concentration would be expected to be comparable between cereals. However, the postprandial increase in the plasma insulin concentration occurred earlier for BC than for CF and resulted in a 76% higher plasma insulin concentration at 20 min and a 125% higher insulin AUC during the 0–30-min postprandial period. In the present study, although the amount of available carbohydrate in the 2 cereals was identical, BC contained ≈ 3.5 times more protein than did CF (15.4 compared with 4.3 g). When protein is added to carbohydrate, insulin secretion and the calculated insulin AUC are augmented (12–14, 23–26); several studies have found that adding protein to carbohydrate attenuates the glycemic response compared with that for carbohydrate alone, in association with a greater insulin response (12, 13, 23, 25, 26). Notably, the addition of ≈ 30 g wheat protein, the type of protein present in BC, to ≈ 59 g carbohydrate resulted in augmented hyperinsulinemia compared with carbohydrate alone (14). Therefore, we believe that in our study the protein-carbohydrate interaction of BC was likely responsible for the more rapid plasma insulin response during the initial 20-min postprandial period.

During the postprandial period, Rd_{glucose} is primarily stimulated by an increase in insulin concentration (11). Rd_{glucose} did not increase above postabsorptive levels for either BC or CF (ie, 30–60 min) until the plasma insulin concentration significantly increased above overnight-fasted concentrations. The markedly earlier insulin response for BC was associated with an earlier increase in Rd_{glucose} , resulting in a 31% higher Rd_{glucose} for BC than for CF during the 30–60-min postprandial period. Importantly, although this was the only time period during which Rd_{glucose} was significantly different between the 2 cereals, this earlier increase in Rd_{glucose} is what attenuated hyperglycemia and the GI of BC. Individuals with impaired glucose tolerance show a delayed rise in postprandial insulin secretion compared with insulin-sensitive control subjects (27, 28). When the delayed rise in plasma insulin concentration is corrected through early insulin supplementation, abnormal hyperglycemia is corrected, in parallel with an earlier increase in Rd_{glucose} (27, 28). Although we saw no significant difference in the insulin AUC over the 180-min postprandial period, it is the markedly earlier rise in plasma insulin concentration seen for BC that appears functionally important for increasing Rd_{glucose} early in the postprandial period, thereby reducing the postprandial hyperglycemia.

The important role of insulin in increasing glucose extraction from the blood is further supported by the GCR, which provides an indication of insulin-mediated glucose uptake by tissue (11). In the present study, the GCR increased above fasting levels during the 30–60-min period with BC only, being 54% higher than that for CF. In parallel with the delayed insulin response with CF, an increase in the GCR was delayed with CF until the 60–90-min period. Interestingly, this temporal delay of ≈ 30 min between insulin appearance in plasma and insulin metabolic action (as indicated by the increased GCR) has been extensively described (29). Furthermore, Carey et al (30) found that the rate of postprandial muscle glycogen storage, an indirect measure of plasma glucose uptake, was significantly correlated with the initial plasma insulin

response ($r = 0.87$). Similarly, we found a strong correlation ($r = 0.71$, $P < 0.009$) between the 30–60-min GCR and the initial plasma insulin response (ie, 0–30-min insulin AUC), further supporting the importance of the early insulin response in increasing plasma glucose removal from the circulation and consequently in attenuating postprandial hyperglycemia.

The concept of GI is based primarily on the interpretation of the glycemic curve and in some instances the relation between the in vivo postprandial glycemic curve and in vitro measurements of glucose availability (31, 32). Although we appreciate that not all foods have a low GI as a result of a greater Rd_{glucose} , we have highlighted herein that the plasma glucose concentration and the GI are indeed a function of both Ra_{glucose} and Rd_{glucose} . It is therefore perhaps tenuous to draw conclusions regarding the “behavior,” and hence the therapeutic applicability, of a food solely from plasma glucose and insulin concentrations without appropriate support from measures of glucose kinetics. Indeed, if we did not directly determine the glucose kinetics of BC and CF, then we would be uncertain whether the lower glycemic response of BC than of CF was due to a reduced Ra_{glucose} secondary to its high fiber content or to enhanced Rd_{glucose} secondary to an earlier increase in plasma insulin concentration. Further research with the use of isotope methods to quantify the plasma glucose kinetics of a broader range of foods, in particular foods containing different types of carbohydrate and different amounts of fat and protein, is necessary to further expand the functional usefulness of the GI. It is also important to frequent blood sampling during the initial 30 min of the postprandial period (eg, every 10 min) for assessment of plasma insulin concentrations because it is the first-phase insulin response, and not necessarily the total AUC, that seems important in attenuating postprandial hyperglycemia and hence the GI.

In conclusion, to our knowledge, this is the first study to systematically investigate the underlying glucose kinetics responsible for the different glycemic response of 2 popular, commercially available foods of low and high GI. The high fiber content of BC did not appear to affect glucose absorption into the systemic circulation, because Ra_{glucose} was not significantly different between the 2 cereals. Despite a comparable Ra_{glucose} , the glycemic response of CF was more than twice that of BC. Instead, the lower postprandial glycemia in BC was due to an augmented Rd_{glucose} during the 30–60-min period in association with an earlier and significantly greater insulin response during the initial 20-min period. Overall, the present findings further the concept of the GI by emphasizing that differences in Rd_{glucose} and not just Ra_{glucose} can account for differences in GI between foods. 

We thank the subjects for their enthusiastic participation and Steven L Walker for his expertise with blood preparation and handling. EFC is a member of the Gatorade Sport Science Institute. None of the other authors had any industry or board affiliations.

SS, CJD, and ECF were involved in the design of the experiment. SS and CJD undertook the data collection. SS performed all data analysis with assistance from CJD (plasma glucose and insulin) and TWZ (plasma glucose, glucose tracer, and calculations). LOB supervised and provided technical expertise in mass-spectrometry analysis of the glucose tracer and calculations. SS was the primary writer of the manuscript. ECF served as laboratory director and supervising professor and also oversaw the writing of the manuscript.

REFERENCES

- Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* 1981;34:362–6.
- Wolever TMS, Jenkins DJA, Jenkins AL, Josse RG. The glycemic index: methodology and clinical implications. *Am J Clin Nutr* 1991; 54:846–54.
- Jenkins DJ, Wolever TM, Jenkins AL, Josse RG, Wong GS. The glycaemic response to carbohydrate foods. *Lancet* 1984;2:388–91.
- Jenkins DJA, Kendall CWC, Augustin LSA, et al. Glycemic index: overview of implications in health and disease. *Am J Clin Nutr* 2002; 76(suppl):266S–73S.
- Jenkins DJ, Thorne MJ, Camelon K, et al. Effect of processing on digestibility and the blood glucose response: a study of lentils. *Am J Clin Nutr* 1982;36:1093–101.
- Thorne MJ, Thompson LU, Jenkins DJ. Factors affecting starch digestibility and the glycemic response with special reference to legumes. *Am J Clin Nutr* 1983;38:481–8.
- Wolever TMS, Katzman-Relle L, Jenkins AL, Vuksan V, Josse RG, Jenkins DA. Glycaemic index of 102 complex carbohydrate foods in patients with diabetes. *Nutr Res* 1994;14:651–69.
- Bjorck I, Granfeldt Y, Liljeberg H, Tovar J, Asp NG. Food properties affecting the digestion and absorption of carbohydrates. *Am J Clin Nutr* 1994;59(suppl):699S–705S.
- Ellis PR, Rayment P, Wang Q. A physiochemical perspective of plant polysaccharides in relation to glucose absorption, insulin secretion and the entero-insular axis. *Proc Nutr Soc* 1996;55:881–98.
- Normand S, Khalfallah Y, Louche-Pelissier C, et al. Influence of dietary fat on postprandial glucose metabolism (exogenous and endogenous) using intrinsically ^{13}C -enriched durum wheat. *Br J Nutr* 2001;86:3–11.
- DeFronzo RA, Ferrannini E. Influence of plasma glucose and insulin concentration on plasma glucose clearance in man. *Diabetes* 1982; 31:683–8.
- Floyd JC, Fajans SS, Pek S, Thiffault CA, Knopf RF, Conn JW. Synergistic effect of essential amino acids and glucose upon insulin secretion in man. *Diabetes* 1970;19:109–15.
- Nuttall FQ, Mooradian AD, Gannon MC, Billington C, Krezowski P. Effect of protein ingestion on the glucose and insulin response to a standardized oral glucose load. *Diabetes Care* 1984;7:465–70.
- van Loon LJ, Saris WH, Verhagen H, Wagenmakers AJ. Plasma insulin responses after ingestion of different amino acid or protein mixtures with carbohydrate. *Am J Clin Nutr* 2000;72:96–105.
- Robertson MD, Henderson RA, Vist GE, Rumsey RD. Extended effects of evening meal carbohydrate-to-fat ratio on fasting and postprandial substrate metabolism. *Am J Clin Nutr* 2002;75:505–10.
- Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* 2002;76:5–56.
- Steele R. Influences of glucose loading and of injected insulin on hepatic glucose output. *Ann NY Acad Sci* 1959;82:420–30.
- Bergeron R, Kjaer M, Simonsen L, Bulow J, Galbo H. Glucose production during exercise in humans: a-hv balance and isotopic-tracer measurements compared. *J Appl Physiol* 1999;87:111–5.
- Hall SE, Bolton TM, Hetenyi G. The effect of bran on glucose kinetics and plasma insulin in non-insulin-dependent diabetes mellitus. *Diabetes Care* 1980;3:520–5.
- Bach Knudsen KE, Jorgensen H, Canibe N. Quantification of the absorption of nutrients derived from carbohydrate assimilation: model experiment with catheterised pigs fed on wheat- or oat-based rolls. *Br J Nutr* 2000;84:449–58.
- Crapo PA, Reaven G, Olefsky J. Postprandial plasma-glucose and -insulin responses to different complex carbohydrates. *Diabetes* 1977; 26:1178–83.
- Horowitz JF, Coyle EF. Metabolic responses to preexercise meals containing various carbohydrates and fat. *Am J Clin Nutr* 1993;58: 235–41.

23. Zawadzki KM, Yaspelkis BB, Ivy JL. Carbohydrate-protein complex increases the rate of muscle glycogen storage after exercise. *J Appl Physiol* 1992;72:1854–9.
24. Day JL, Johansen K, Ganda OP, Soeldner JS, Gleason RE, Midgley W. Factors governing insulin and glucagon responses during normal meals. *Clin Endocrinol* 1978;9:443–54.
25. Spiller GA, Jensen CD, Pattison TS, Chuck CS, Whittam JH, Scala J. Effect of protein dose on serum glucose and insulin response to sugars. *Am J Clin Nutr* 1987;46:474–80.
26. Gannon MC, Nuttall FQ, Neil BJ, Westphal SA. The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. *Metabolism* 1988;37:1081–8.
27. Bruce DG, Chisholm DJ, Storlien LH, Kraegen EW. Physiological importance of deficiency in early prandial insulin secretion in noninsulin-dependent diabetes. *Diabetes* 1988;37:736–44.
28. Uchino H, Niwa M, Shimizu T, Nishiyama K, Kawamori R. Impairment of early insulin response after glucose load, rather than insulin resistance, is responsible for postprandial hyperglycemia seen in obese type 2 diabetes: assessment using nateglinide, a new insulin secretagogue. *Endocr J* 2000;47:639–41.
29. Natali A, Gastaldelli A, Camastra S, et al. Dose-response characteristics of insulin action on glucose metabolism: a non-steady-state approach. *Am J Physiol* 2000;278:E794–801.
30. Carey PE, Halliday J, Snaar JE, Morris PG, Taylor R. Direct assessment of muscle glycogen storage after mixed meals in normal and type 2 diabetic subjects. *Am J Physiol* 2003;284:E688–94.
31. Jenkins DJ, Ghafari H, Wolever TM, et al. Relationship between rate of digestion of foods and post-prandial glycaemia. *Diabetologia* 1982;22:450–5.
32. Englyst HN, Veenstra J, Hudson GJ. Measurement of rapidly available glucose (RAG) in plant foods: a potential in vitro predictor of the glycaemic response. *Br J Nutr* 1996;75:327–37.

