Colonic fermentation of indigestible carbohydrates contributes to the second-meal effect[1–4]

Furio Brighenti, Luigi Benini, Daniele Del Rio, Cristina Casiraghi, Nicoletta Pellegrini, Francesca Scazzina, David JA Jenkins, and Italo Vantini

ABSTRACT

Background: Low postprandial blood glucose is associated with low risk of metabolic diseases. A meal's ability to diminish the glucose response to carbohydrates eaten during the following meal is known as the "second-meal effect" (SME). The reduced glycemia elicited by low-glycemic-index (LGI) foods consumed during the first meal has been suggested as the main mechanism for SME. However, LGI foods often increase colonic fermentation because of the presence of fiber and resistant starch.

Objective: The objective was to study the SME of greater fermentation of high-glycemic-index (HGI) and LGI carbohydrates eaten during a previous meal.

Design: Ten healthy volunteers ate 3 breakfast test meals consisting of sponge cakes made with rapidly digestible, nonfermentable amylopectin starch plus cellulose (HGI meal), amylopectin starch plus the fermentable disaccharide lactulose (HGI-Lac meal), or slowly digestible, partly fermentable amylose starch plus cellulose (LGI meal). Five hours later, subjects were fed the same standard lunch containing 93 g available carbohydrates. Blood was collected for measurement of glucose, insulin, and nonesterified fatty acids (NEFAs). Breath hydrogen was measured as a marker of colonic fermentation. Postlunch gastric emptying was measured by using ultrasonography.

Results: Both the HGI-Lac and LGI meals improved glucose tolerance at lunch. In the case of the HGI-Lac meal, this effect was concomitant with low NEFA concentrations and delayed gastric emptying.

Conclusion: Fermentable carbohydrates, independent of their effect on a food's glycemic index, have the potential to regulate postprandial responses to a second meal by reducing NEFA competition for glucose disposal and, to a minor extent, by affecting intestinal motility. *Am J Clin Nutr* 2006;83:817–22.

KEY WORDS Second-meal effect, glycemic index, colonic fermentation, dietary fiber, lactulose

INTRODUCTION

Diets based on foods that can reduce postprandial blood glucose excursions [ie, fiber-rich foods with a low glycemic index (GI)] are receiving increasing attention regarding their ability to reduce the risk of diseases related to impaired glucose metabolism (1). Encouraging results were reached by the use of low-GI (LGI) foods to improve glucose tolerance, both immediately after consumption and at the subsequent meal. The action of different amounts of glucose on the metabolism of a subsequent intake of carbohydrates in humans was first observed in the early part of the 20th century (2, 3), but the involvement of glucose bioavailability as a factor influencing the postprandial response of the second load was taken into account only in the latter part of that century. Jenkins et al (4) and Wolever et al (5) described this phenomenon as "the second-meal effect" (SME) and identified the GI of the meal preceding the second meal as the determinant of the improved glucose tolerance observed at the subsequent food consumption.

In these studies, an LGI was associated with larger amounts of fermentable dietary fiber than was a high GI (HGI). This fact opens the possibility that, at least in part, colonic fermentation of indigestible carbohydrates could be a further mechanism involved in reduced glycemia during the second meal.

The current work was designed to study the SME of different types of breakfast meals. In particular, the SME of a completely and rapidly digestible breakfast containing amylopectin starch with or without added the fermentable disaccharide lactulose was compared with that of a slowly digestible breakfast meal containing high-amylose starch, in which, besides being slowly digested, some of the starch would escape small-intestine digestion and be fermented in the colon. These breakfast meals were prepared and studied to investigate which component (GI, fermentability, or both) might contribute to the SME.

[1] From the Human Nutrition Unit, Department of Public Health, University of Parma, Parma, Italy (FB, DDR, NP, and FS); the Department of Biomedical and Surgical Sciences, University of Verona, Verona, Italy (LB and IV); the Department of Food Science and Technology, University of Milan, Milan, Italy (CC); and the Clinical Nutrition and Risk Factor Modification Center, St Michael's Hospital, Toronto, Canada (DJAJ).

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[4] Reprints not available. Address correspondence to F Brighenti, Department of Public Health, University of Parma, Via Volturno 39, 43100, Parma, Italy. E-mail: furio.brighenti@unipr.it.

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SUBJECTS AND METHODS

Subjects

Ten healthy volunteers (n = 8 men and 2 women) aged 40 ± 10 y and with a normal body mass index [(in kg/m^2) 23.7–3.2] participated in the study. The subjects were not taking medications, were not lactose intolerant, did not have diarrhea, and had not taken antibiotics for 3 mo before the study period. All subjects were asked to avoid smoking during the test day and to maintain their usual pattern of physical activity during the study period. The dinner before each study day was standardized for quantity and quality of food items (low-fiber and HGI carbohydrate sources) for all the subjects and before each test.

Subjects gave written informed consent. The study was performed in accordance with the principles of the 1993 Declaration of Helsinki and approved by the ethics committee of the University of Verona.

Test meals

Three types of breakfast meal, varying in the type of starch and dietary fiber used in the recipe, were prepared. All of the breakfast meals consisted of a sponge cake (140–175 g available carbohydrates) and 250 mL unsweetened black tea. Cakes were prepared with starch, sucrose, table salt, butter, purified dietary fiber, eggs, flavors, and leavening agents according to a standard recipe and baked for 35 min at 180 °C (**Table 1**). Two cakes were prepared by using a quickly and completely digestible amylopectin corn starch (AMIOCA; National Starch & Chemicals SpA, Milan, Italy), which was the HGI starch. One cake was prepared by using a slowly digestible and partially fermentable amylose corn starch (HYLON VII; National Starch & Chemicals SpA), which was the LGI starch. The purified fiber used for the LGI breakfast and for 1 of the 2 HGI breakfasts was a preparation of nonfermentable purified cellulose from hazelnut shells (ALSO, Zelbio, Italy), whereas, in the second HGI breakfast, the HGI-Lac meal, cellulose was replaced with 5 g of the undigestible and highly fermentable disaccharide lactulose in crystalline form (INALCO, Milan, Italy).

TABLE 1
Composition of test breakfast and standard lunch meals[1]

	Amount
Ingredients of the meal	
Breakfast	
Starch source (g)	60
LGI breakfast: amylose	60
HGI and HGI-Lac breakfasts: amylopectin	60
Sucrose (g)	15
Egg (g)	87
Salt (g)	0.5
Butter (g)	10
Fiber source (g)	5
LGI and HGI breakfasts: cellulose	5
HGI-Lac breakfast: lactulose	5
Lunch	
Pasta (g)	70
Bolognese sauce (g)	35
White bread (g)	50
Cheese (g)	25
Ham (g)	30
Nutrient composition	
Breakfast	
Energy (kcal)	480
Available carbohydrate[2] (g)	75[3]
Total starch (g)	55
LGI breakfast: resistant starch (g)	13
HGI and HGI-Lac breakfasts: resistant starch (g)	1
Protein (g)	10
Fat (g)	17
Dietary fiber (g)	5
Lunch	
Energy (kcal)	715
Available carbohydrate[2] (g)	93
Protein (g)	28
Fat (g)	28
Dietary fiber (g)	4

[1] HGI, high-glycemic-index starch + cellulose breakfast; LGI, low-GI starch + cellulose breakfast; HGI-Lac, HGI starch + lactulose breakfast.
[2] Available carbohydrate in monomeric form.
[3] Including resistant starch.

Study protocol

Breakfasts were fed to the subjects once a week in random order. Five hours after consuming breakfast, subjects were fed a 715-kcal standard meal (93 g available carbohydrates) consisting of pasta with Bolognese sauce, white bread, ham, cheese, and 200 mL mineral water (Table 1). During each test day, blood was collected every 30 min for the first 2 h after breakfast, then every 60 min until lunch, then every 30 min for the first 2 h after lunch, and then every 60 min to a total collection time of 10 h. Breath-hydrogen production was quantified hourly throughout the study as a marker of colonic fermentation. In addition, the gastric emptying rate (GER) was measured for 5 h after consumption of the second meal.

Blood collection and analyses

At each timepoint, 5 mL of venous blood was collected (by means of a indwelling cannula kept patent with the use of a saline drip) for the measurement of plasma glucose, insulin, and nonesterified fatty acids (NEFAs); the blood was stored at −20 °C (for glucose measurements) or −80 °C (for insulin and NEFA measurements) until analysis. Blood glucose concentrations were measured by using a semiautomatic glucose and lactate analyzer (STAT 2300; YSI, Yellow Springs, OH). Plasma insulin concentrations were measured by using a radioimmunoassay (Abbott SpA, Latina, Italy). Plasma free fatty acids were quantified by using a specific enzymatic kit (NEFA C enzymatic, ACS-ACOD END; Italfarmaco, Milan, Italy).

Breath-hydrogen test

Breath was collected with the use of a specific breath-collection system (GaSampler; Quintron Instruments, Milwaukee, WI), and 30 mL of each breath sample was maintained in a sealed, gas-tight syringe for a maximum of 2 h before analysis. Hydrogen quantification was performed by using a hydrogen analyzer (Clinical MicroLyzer 2; Quintron Instruments) that was calibrated with a mixture of 102 ppm hydrogen in air (SIO, Bergamo, Italy).

Measurement of gastric emptying rate

The GER was assessed by using real-time ultrasonography (SSA-220A ultrasonographer; Toshiba Diagnostic Equipment,

Rome, Italy) according to the procedure described by Benini et al (6). Measurements were made before the second meal (basal measurement), immediately after ingestion (*t*0 measurement), at 30-min intervals for the first 2 h, and at 1-h intervals thereafter. The mean of 3 readings was calculated at each time during interperistaltic relaxation. The antral section was calculated by using the formula

$$S = d_1 \times d_2 \times \pi/4 \qquad (1)$$

where S represents the antral cross-sectional area and d_1 and d_2 represent the measured diameters. The antral cross-sectional area was then plotted against the time. The ultrasonographic half emptying times were identified by linear regression and used for the statistical analysis.

Statistical analysis

Results are given as means ± SEMs. To assess the effect of treatment, the postbreakfast and postlunch glucose, insulin, and NEFA profiles were submitted to 2-factor repeated-measures analysis of variance, in which treatment was the repeated measure and time was the independent factor. When the time × treatment interaction was significant, differences among treatments at single timepoints were assessed by using repeated-measures ANOVA and then Tukey's honestly significant differences post hoc test. The same tests were performed to assess differences in breath-hydrogen and gastric half-emptying times. Areas under the curve (AUC) for NEFA during period after the second meal were calculated by using the trapezoidal rule. Differences among AUCs were assessed by using repeated-measures ANOVA and then Tukey's honestly significant differences post hoc test. The relation between gastric half-emptying time and the time of glucose peak or area under the glucose curve of the second meal was assessed by using Spearman's rank correlation. STATISTICA software (version 4.5; Stat-Soft Inc, Tulsa, OK) was used on a personal computer for all statistical analyses.

RESULTS

Glucose

The glucose responses after the test meals are shown in **Figure 1**. Meals gave significantly different glucose profiles over the study period (effect of treatment, $P < 0.005$; time × treatment interaction, $P < 0.02$). The LGI breakfast, which was made with amylose starch, gave lower GIs immediately after consumption, as expected. In particular, the single timepoint at 30 min after the LGI breakfast was significantly ($P < 0.03$) lower than that after both the HGI and HGI-Lac breakfasts. During the postlunch period preceded by the LGI breakfast, glucose values significantly ($P < 0.05$) lower than those after the HGI breakfast were seen at the 9th hour. During the postbreakfast period, the HGI-Lac breakfast, which included amylopectin starch and lactulose, gave a glycemic response comparable to that after the HGI breakfast, but, during the postlunch period, it resulted in lower glycemic profiles, similar to those obtained after the LGI breakfast but significantly different from those after the HGI breakfast, at the 8th ($P < 0.01$) and 9th ($P < 0.05$) hours.

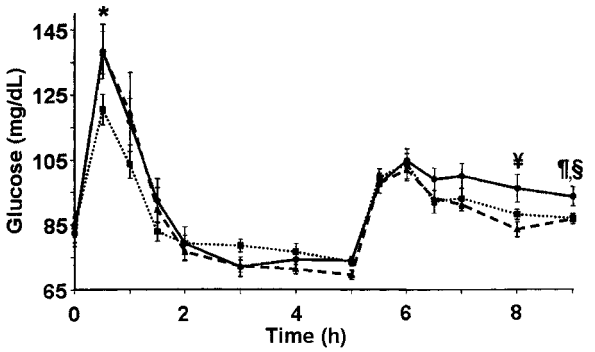

FIGURE 1. Mean (±SE) glucose concentrations during the test period after the high-glycemic-index (HGI; ●), low-glycemic-index (LGI; ■), and HGI with lactulose (HGI-Lac; ▲) breakfasts. $n = 10$. Effect of treatment, $P < 0.005$; time × treatment interaction, $P < 0.02$ (both: repeated-measures ANOVA). $^{*}P < 0.03$: differences between the HGI and HGI-Lac breakfasts and between the HGI and LGI breakfasts; $^{¥}P < 0.01$: difference between the HGI and HGI-Lac breakfasts; $^{§}P < 0.05$: difference between the HGI and LGI breakfasts; $^{¶}P < 0.05$: difference between the HGI and HGI-Lac breakfasts (all: Tukey's honestly significant differences post hoc test).

Insulin

Insulin responses after the test meals are shown in **Figure 2**. Significantly different insulin profiles throughout the study period (time × treatment interaction, $P < 0.005$) were entirely accounted for by differences elicited by LGI during the postbreakfast phase. In particular, the LGI breakfast gave lower plasma insulin values after 1 ($P < 0.02$) and 2 ($P < 0.05$) h than did the HGI breakfast and lower values after 1 h ($P < 0.03$) than did the HGI-Lac breakfast, which in turn was almost equivalent to the values with the HGI breakfast throughout the test period.

Nonesterified fatty acids

NEFA responses after the test meals are shown in **Figure 3**. NEFA profiles also differed significantly throughout the study period (effect of treatment, $P < 0.01$). In particular, NEFA concentration after the HGI-Lac breakfast was significantly lower than that after the HGI ($P < 0.03$) and LGI ($P < 0.01$, Tukey post hoc test) breakfasts (Figure 3). During the postlunch period, treatments resulted in significantly different NEFA AUCs ($P <$

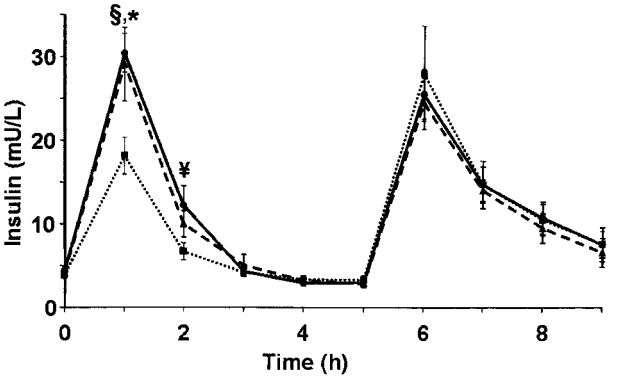

FIGURE 2. Mean (±SE) insulin concentrations during the test period after the high-glycemic-index (HGI; ●), low-glycemic-index (LGI; ■), and HGI with lactulose (HGI-Lac; ▲) breakfasts. $n = 10$. Time × treatment interaction, $P < 0.005$ (repeated-measures ANOVA). $^{§}P < 0.02$: difference between the HGI and LGI breakfasts; $^{¥}P < 0.05$: difference between the HGI and LGI breakfasts; $^{*}P < 0.03$: difference between the LGI and HGI-Lac breakfasts (all: Tukey's honestly significant differences post hoc test).

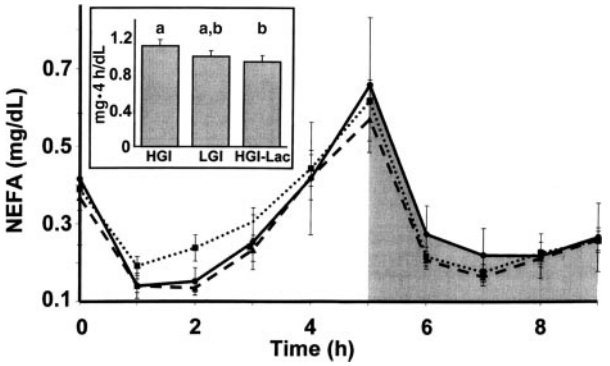

FIGURE 3. Mean (±SE) nonesterified fatty acid (NEFA) concentrations during the test period after the high-glycemic-index (HGI; ●), low-glycemic-index (LGI; ■), and HGI with lactulose (HGI-Lac; ▲) breakfasts. $n = 10$. Effect of treatment, $P < 0.01$ (repeated-measures ANOVA). The NEFA concentrations after the HGI-Lac breakfast were significantly lower than those after the HGI ($P < 0.03$) and LGI ($P < 0.01$) breakfasts (all: Tukey's post hoc test). The box represents the postlunch area under the curve (AUC) for the 3 breakfasts (shaded area in figure). During the postlunch period, treatments resulted in significantly different NEFA AUCs ($P < 0.02$). Bars with different letters are significantly different, $P < 0.05$ (repeated-measures ANOVA followed by Tukey's honestly significant differences post hoc test); in particular, the HGI breakfast gave significantly higher postlunch AUC values than did the HGI-Lac breakfast ($P < 0.02$) but not significantly higher postlunch AUC values than did the LGI breakfast ($P = 0.1$; Tukey's post hoc test).

0.02) (Figure 3, box). In this case, both the HGI-Lac and LGI AUCs were lower than the HGI AUC, although only the HGI-Lac AUC was significantly ($P < 0.02$, Tukey's post hoc test) lower than the HGI AUC; the HGI-Lac and LGI AUCs did not differ significantly ($P = 0.541$).

Breath-hydrogen test

Molecular hydrogen concentrations are shown in **Figure 4**. Meals gave significantly different hydrogen profiles over the study period (effect of treatment, $P < 0.0001$; time × treatment interaction, $P < 0.0001$). Values were virtually identical for all 3 types of breakfast during the first part of the study period. We observed no hydrogen increase from the completely digestible HGI breakfast during the postlunch period. On the contrary, the

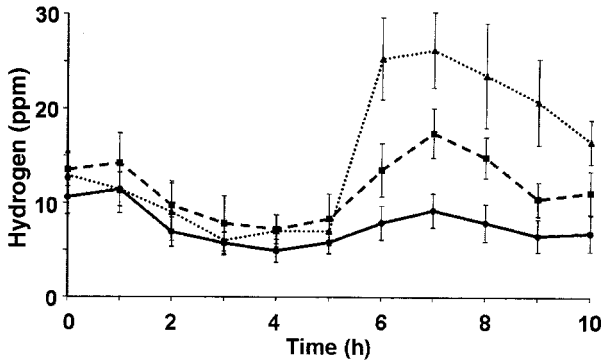

FIGURE 4. Mean (±SE) breath-hydrogen concentrations during the test period after the high-glycemic-index (HGI; ●), low-glycemic-index (LGI; ■), and HGI with lactulose (HGI-Lac; ▲) breakfasts. $n = 10$. Effect of treatment, $P < 0.0001$; effect of time × treatment interaction, $P < 0.0001$ (both: repeated-measures ANOVA); all of the points differed significantly ($P < 0.001$) between treatments starting from the 6th hour (Tukey's honestly significant differences post hoc test).

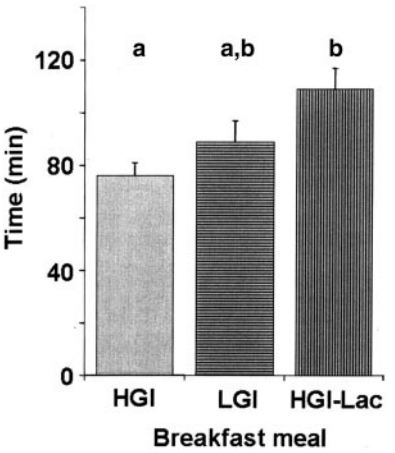

FIGURE 5. Mean (±SE) ultrasonographic gastric half-emptying times (min) of the second meal preceded by the different breakfast meals. $n = 10$. Bars with different letters are significantly different, $P < 0.05$ (repeated-measures ANOVA followed by Tukey's honestly significant differences post hoc test).

LGI breakfast slightly but significantly increased the H_2 values beginning in the 6th hour and extending to the end of the study ($P < 0.001$ for each time in comparison to the HGI breakfast). The same effect was observed, to a greater extent, after the HGI-Lac breakfast, which from the 6th hour resulted in H_2 values significantly higher than those of both the HGI and LGI breakfasts (both: $P < 0.001$ for each time). The average peak H_2 values of ≈18 and ≈26 ppm reached at the 7th hour for LGI and HGI-Lac, respectively were in keeping with the expected degree of fermentation of the resistant starch and lactulose consumed during breakfast (7, 8).

Gastric emptying rate

The gastric half-emptying times measured after the second meal preceded by the 3 different types of breakfast are shown in **Figure 5**. The LGI and HGI-Lac breakfasts led to a slower GER during lunchtime than did the HGI breakfast, but only that with the HGI-Lac breakfast differed significantly from that with the HGI breakfast ($P < 0.05$).

DISCUSSION

Almost a century ago, Staub (2) and Traugott (3) reported independently that a first glucose load may improve the glycemic response of a subsequent glucose load consumed within 12 h. In the 1980s, Jenkins et al (4) and Wolever et al (5) observed that not only the glucose amount but also its bioavailability can influence glucose tolerance at the following meal. In particular, if the first meal has an LGI, the response to the subsequent glucose load is lowered and vice versa. This phenomenon was named the "second-meal effect."

The metabolic benefit of decreasing the rate of glucose absorption was clearly shown by studying the effect of 50 g glucose in water consumed either over 5–10 min (bolus) or at a constant rate over 3.5 h (sipping), as described by Jenkins et al (9). In the latter case, enhanced insulin economy and glucose disposal were observed during an intravenous-glucose-tolerance test administered 4 h later. However, even though these findings strongly suggest that prolonged glucose absorption itself plays a role in

the SME, such a model (glucose + intravenous-glucose-tolerance test) cannot give information about other potential mechanisms related to enteral nutrition, such as colonic fermentation that might contribute to the SME when real foods are consumed. Indeed, LGI foods are often a source of soluble dietary fiber, which can both reduce glucose absorption and stimulate colonic fermentation. The original studies of Jenkins et al (4) and Wolever et al (5) were able to show the SME when lentils and barley, 2 LGI foods rich in soluble and fermentable fiber, were consumed as the first meal but not when that meal consisted of wholemeal bread, an HGI food rich in nonfermentable fiber. Furthermore, the addition of the viscous and fermentable fiber guar gum to a glucose load can induce an SME (10, 11). The question, then, arises: Are fermentable carbohydrates simply bystanders of the SME of LGI foods, or may mechanisms linked to fermentation also play a role?

We have tried to distinguish the effect of GI from that of colonic fermentation by exploring 2 different approaches. We enhanced the colonic fermentation of an HGI amylopectin breakfast meal by adding lactulose, a soluble disaccharide that boosts colonic fermentation but that, because it is nonviscous, should not affect the GI of the food to which is added. We also both increased fermentation and decreased the GI of the breakfast meal by replacing amylopectin with amylose, a slowly and incompletely digestible starch fraction. Osmotic agents, such as the disaccharide lactulose, may shorten intestinal transit time, which will affect nutrient absorption (12). Therefore, to prevent the risk of a possible confounding effect on the rate of glucose absorption, we limited the amount of lactulose to the minimum (5 g) that has been shown to significantly increase colonic fermentation without altering the orocecal transit time of a solid meal (7, 8). The amount of lactulose used by us is far below the 20 g lactulose used by Ropert et al (13) to affect proximal gut motility and gastric tone, but Piche et al (14) obtained more relaxation of the lower esophageal sphincter with only 6.6 g fructooligosaccharide, a substrate similar to lactulose in its rate and extent of fermentation. Moreover, Lin et al (15) reported a significant delay in the gastric emptying of a second meal by feeding during the first meal as little as 125 g lentils, containing ≈2 g soluble fiber (16) and 3.5 g oligosaccharides (17), which corresponds to a total fermentable carbohydrate load of a little more than 5 g. The amount of lactulose used in the current study is not significantly different from that value.

Our results show that, when used as the only starch source, amylose could reduce postprandial glycemic and insulinemic responses more than did amylopectin. This observation may be explained by the well-known slow digestibility of amylose and may be confirmed by data in the literature (18–20). However, lactulose had no effect in reducing glycemic and insulinemic responses after consumption of the amylopectin breakfast meal, which confirmed that the dose of lactulose used could not hamper glucose availability when added to an HGI starch meal. Nonetheless, both amylose and lactulose breakfasts were effective in improving the glucose tolerance of a second meal. Moreover, in both cases, insulin values were equivalent after the second meal, whereas circulating free fatty acids were reduced (although significantly so after the HGI-Lac breakfast only), which suggests that both the LGI and the HGI-Lac breakfasts could have effectively improved insulin sensitivity. The differences in glucose concentrations, although significant, were not impressive (≈5 mg/dL at 8 and 9 h, respectively). However, it is noteworthy that such differences were obtained after a second meal containing 93 g carbohydrate, half of which was derived from an LGI food (pasta). Nonetheless, they were virtually identical to those found by Jenkins et al (≈5.5 mg/dL) after a second meal containing 100 g carbohydrates from HGI sources (bread and banana) that was preceded by a fermentable carbohydrate load from lentils estimated by the breath-hydrogen test to be 16 g (4). The LGI breakfast rich in amylose may have exerted its effect partly by ameliorating the preprandial metabolic status of the second meal, as originally suggested by Jenkins et al (4) and Wolever et al (5), but this possibility is excluded in the case of the HGI-Lac breakfast. Conversely, both meals that elicited the SME also could significantly increase breath H_2 concentration starting from 6 h after consumption, which suggests a common mechanism linked to colonic fermentation. Similarly, Robertson et al (21) showed that amylose-resistant starch enhances carbohydrate handling in the postprandial period at a distance of >12 h, which suggests that the effect could be due to colonic fermentation.

In this respect, some attention has been directed to colonic fermentation products, such as organic acids, that accompany gas production when carbohydrates are fermented in the colon. Ostman et al (22) showed that lactic acid added to bread eaten at breakfast was able to significantly reduce the glycemic and insulinemic responses to an HGI lunch meal consumed 4 h later. Organic acids, and especially short-chain fatty acids (SCFAs), can also acutely reduce the postprandial gycemic response. Brighenti et al (23) observed a marked reduction in the glycemic response when 75 g bread was consumed with acetic acid (16 mmol from vinegar). Rectal infusion of sodium acetate and propionate in amounts similar to those produced by fermentation of dietary fiber decreases serum NEFA in 2 h (24), which indicates that SCFAs of colonic origin may have an effect on glucose metabolism by reducing competition between glucose and fat oxidation. Another hypothesis is that SCFAs produced by colonic fermentation of carbohydrates may be mediators of gastric motility, as originally described by Ropert et al (13). They showed that both lactulose-induced colonic fermentation and intracolonic infusion of SCFAs could reduce gastric tone. Piche et al (14) observed colonic fermentation–mediated lower esophageal sphincter relaxation, and they hypothesized that a neural mechanism was responsible for the action of SCFAs on muscular tone. This hypothesis was later disproved by Cuche et al (25), who observed the involvement of a clear humoral mechanism in SCFA action by using innervated and denervated ileal loops in pigs. Nonetheless, the inhibitory substance involved in this humoral mechanism that may be linked to colonic fermentation is still putative, even though several observations led us to consider a possible involvement of incretins such as polypeptide YY and glucagon-like peptides (25–27). In the current study, a slower gastric emptying of the second meal was observed according to the fermentation profile, which suggested that a release of SCFAs during fermentation could have affected gastric motility. However, gastric emptying was significantly delayed only by lactulose, and amylose was marginally effective. Moreover, neither the glucose peak time nor the incremental area under the glucose curve were significantly correlated with GERs in the study subjects ($P = 0.585$ and $= 0.335$, respectively), which suggests that inhibition of gastric motility had only a secondary effect, if any, on the SME. In conclusion, our results show that fermentable carbohydrates, independent of their effect on food GI, have the potential to improve postprandial responses to a

second meal by decreasing NEFA competition for glucose disposal and, to a minor extent, by affecting intestinal motility. The potential of fermentable carbohydrates in the management of metabolic disorders linked to insulin resistance (28) may warrant further study.

FB, LB, CC, and IV were involved in the study conception, design, and analysis; FB and DDR wrote the manuscript and provided significant advice and consultation; FS, NP, and DJAJ helped analyze and interpret the data and critically revised the manuscript. None of the authors had any personal or financial conflict of interest.

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