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Resistant Starch and Pullulan Reduce Postprandial Glucose, Insulin, and GLP-1, but Have No Effect on Satiety in Healthy Humans

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ABSTRACT: The aim of this study was to determine the effects of three novel fibers on satiety and serum parameters. In a randomized, double-blind, crossover design, fasted subjects (n = 20) consumed a low-fiber control breakfast or one of four breakfasts containing 25 g of fiber from soluble corn fiber (SCF) or resistant starch (RS), alone or in combination with pullulan (SCF+P and RS+P). Visual analog scales assessed appetite, and blood samples were collected to measure glucose, insulin, ghrelin, and glucagon-like peptide-1 (GLP-1). The fiber treatments did not influence satiety or energy intake compared to control. RS+P significantly reduced glucose, insulin, and GLP-1, but neither SCF treatment differed from control. To conclude, these fibers have little impact on satiety when provided as a mixed meal matched for calories and macronutrients. Additional research regarding the physiological effects of these novel fibers is needed to guide their use as functional ingredients in food products.

KEYWORDS: *fiber, satiety, gut hormones, glucose, visual analog scale*

INTRODUCTION

Fiber consumption is inversely associated with body weight, body fat, and body mass index (BMI) in cross-sectional studies, and fiber supplementation has been shown to improve weight loss in intervention trials.[1−5] A number of reviews have summarized the ability of dietary fiber to increase satiety and reduce energy intake.[6−8] However, variability in the literature on this topic makes generalizations difficult, and it is clear not all fibers are equally satiating.[9,10] Characteristics of the fiber (e.g., solubility, fermentability, and viscosity), dose, duration of intake, and how the fiber is consumed may all influence the level of satiety achieved.

The mechanism by which fiber may affect satiety is not clear, but may be related to changes in appetite-related gut hormones. A number of peptides, including glucagon-like peptide-1 (GLP-1), have been shown to increase satiety and decrease energy intake in humans.[11] Conversely, ghrelin is known to stimulate hunger and energy intake.[12] Although many studies evaluate changes in gut hormone concentrations following intake of carbohydrates, fats, and protein, few well-controlled studies measure changes in these hormones after fiber consumption.

Fiber may also influence satiety via effects on postprandial glucose and insulin concentrations. Certain fibers can delay gastric emptying and nutrient absorption, thus slowing delivery of glucose into the bloodstream.[13,14] Some research suggests that foods that produce a slower, sustained glucose response are associated with increased satiety,[15,16] although not all research supports this relationship.[17,18]

Epidemiological data indicate that high postprandial glucose concentrations are an independent risk factor for cardiovascular disease in individuals with diabetes[19,20] and are associated with mortality from cardiovascular disease as well as all-cause mortality in nondiabetic men and women.[21,22] Therefore, dietary strategies to reduce the glycemic response to a meal may be useful for the prevention or management of diabetes and cardiovascular disease. Addition of fiber to food products may improve glycemic response and have beneficial effects on risk factors for chronic disease.[23]

Fiber intake is low in the United States, with most individuals consuming only half the recommended levels.[24] In response to this, the addition of functional fibers to new or existing food products has been a growing trend in the food industry. However, little is known regarding the physiological effects of many of these fibers. Thus, the purpose of this study was to evaluate the effects of three novel fibers on glucose, insulin, and gut hormone response and to examine the relationship between these variables and subjective measures of appetite.

MATERIALS AND METHODS

Participant Eligibility. Twenty subjects were recruited via flyers posted around the University of Minnesota campus. Subjects initially completed a telephone screen to determine if they met the inclusion criteria. Eligible subjects were English-speaking, healthy men and women aged 18−60 years, nonsmoking, nondieting (weight stable over the past 3 months), with a BMI between 18.5 and 27 kg/m^2 and with normal fasting blood glucose. Exclusion criteria were as follows: history of disease; gastrointestinal conditions affecting digestion and absorption; use of medications; food allergies to study products; persons who did not regularly consume breakfast; restrained eaters (score >10 on the dietary restraint factor of the Three Factor Eating Questionnaire);[25] vegetarians; individuals who consumed more than approximately 15 g of fiber per day; or women who were pregnant or lactating. This study was approved by the University of Minnesota Institutional Review Board Human Subjects Committee (IRB approval 0701M00264). Written informed consent was obtained from all subjects prior to the start of the study.

Screening and Study Visits. Eligible subjects attended a screening visit at the General Clinical Research Center (GCRC). The study coordinator verified medical history and anthropometric measurements,

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and fasting blood glucose <126 mg/dL was confirmed via finger stick. Subjects were instructed to follow a low-fiber lead-in diet and to avoid fiber supplements, alcohol, and excessive exercise for 24 h before each study visit.

On five separate occasions, subjects arrived at the GCRC following a 12 h fast. Each visit lasted approximately 4 h and was separated by a washout period of at least 3 weeks. Women were only scheduled during the follicular phase of their menstrual cycle, so some visits were more than 3 weeks apart. At the start of each visit, an iv was placed in the antecubital vein, followed by a 10 min break to ensure the stress of venepuncture did not alter baseline hormone concentrations.[26] Study staff then instructed subjects on the use of computerized visual analog scales (VAS), and subjects completed baseline appetite measures. Immediately following completion of the VAS, nursing staff drew baseline blood samples for glucose, insulin, ghrelin, and GLP-1. Subjects then received a low-fiber control breakfast or one of four fiber-containing breakfasts and were instructed to consume the entire meal within 20 min. Participants were not allowed to consume any additional food or water for the duration of the study.

Appetite ratings were recorded by VAS, and blood samples were drawn for glucose and insulin at 15, 30, 45, 60, 90, 120, and 180 min after completion of the test meal. Ghrelin and GLP-1 were assessed at 30 and 60 min after the meal. Subjects rated palatability of the test meal at the 15 min time point. Completion of the VAS always preceded blood sampling. The iv was removed following the 180 min blood draw, and subjects were then offered an ad libitum buffet lunch. The lunch consisted of a variety of preweighed food items, including sandwiches, soup, salad, fresh fruits and vegetables, dessert, and beverages. Subjects were instructed to eat until comfortably full. After 30 min, lunch items were removed and weighed to calculate energy intake. Prior to discharge from the GCRC, a registered dietitian instructed subjects on completing a detailed food record for the remainder of the day.

Test Breakfasts. Subjects consumed the five test breakfasts in a randomized, crossover design. Meals consisted of a muffin, hot cereal, and a fruit-flavored beverage powder mixed into 250 mL of water. The fiber treatments provided 25 g of fiber from soluble corn fiber (SCF) or resistant starch (RS) alone or in combination with 5 g of pullulan (SCF+P and RS+P).

SCF, RS, and pullulan are glucose polymers that are resistant to digestion but differ in physicochemical properties. SCF is formed from the hydrolysis of corn starch by heat and acid, followed by cooling to form a branched structure with both digestible and nondigestible bonds. The RS used in this study was produced from heat−moisture-treated high amylose maize starch. It is insoluble and classified as a type 3 (retrograded) RS. Pullulan is produced from the fermentation of dextrin by *Aureobasidium pullulans*. It is water-soluble and forms a viscous solution when dissolved.

All test products were provided by Tate and Lyle Inc. (Decatur, IL, USA). Treatments were similar in appearance and were matched for calories, macronutrient content, and available carbohydrates (Table 1).

Table 1. Composition of Test Meals[a]

treatment	fiber (g)	fat (g)	protein (g)	calories	available carbohydrate (g)	water (g)
control	2.8	12.7	10.4	591.3	104.9	372.1
SCF	27.8	12.6	10.3	617.1	103.9	347.8
SCF+P	27.8	12.6	10.3	614.1	103.7	347.9
RS	27.2	12.8	10.3	589.4	105.8	349.5
RS+P	27.2	12.8	10.3	586.4	105.7	349.7

[a] Nutrition content listed per test breakfast. All data provided by Tate and Lyle. Treatment materials were analyzed as dietary fiber according to AOAC method 991.43 or AOAC method 2001.03. Other data generated by using accepted AOAC methods.

Muffins were stored at −20 °C and thawed at room temperature for 2 h prior to each subject visit.

Visual Analog Scales. Ratings of hunger, satisfaction, fullness, and prospective food intake were assessed using a previously validated 100 mm VAS.[27] The questions appeared as follows: "How hungry do you feel?" Possible answers ranged from "Not hungry at all" (0 mm) to "I have never been more hungry (100 mm)". "How satisfied do you feel?" "I am completely empty" (0 mm) to "I cannot eat another bite" (100 mm). "How full do you feel?" "Not at all full" (0 mm) to "Totally full" (100 mm). "How much do you think you can eat?" "Nothing at all" (0 mm) to "A lot" (100 mm).

Subjects also completed five VAS questions to assess the palatability of the test breakfasts. Visual appeal, smell, taste, and overall pleasantness were rated from good (0 mm) to bad (100 mm). Aftertaste was rated from much (0 mm) to none (100 mm).

Dietary Intake Analysis. Food records were analyzed using the Nutrition Data System for Research (NDSR, version 2008, Nutrition Coordinating Center, Minneapolis, MN, USA) program for determination of energy, carbohydrate, fat, protein, and fiber intake.

Sample Collection and Analysis. Glucose and insulin were analyzed by the Collaborative Studies Clinical Laboratory at the University of Minnesota Medical Center. Glucose was measured by the hexokinase method (Roche Diagnostics, Indianapolis, IN, USA), and insulin was determined by the double-monoclonal antibody enzyme-linked immunosorbent assay method (Merodia AB, Uppsala, Sweden). Gut hormones were analyzed with commercially available kits from Millipore (St. Charles, MO, USA). Samples for total ghrelin and active GLP-1 were collected and stored according to the manufacturer's instructions.

Statistical Analysis. Subjects were randomized according to a Williams design that balanced treatments over visits and subjects. There were 10 sequences, and the study was stratified so that both genders were assigned to each of the 10 sequences. Subjects were assigned to treatments in order of enrollment. The sample size for this study was chosen on the basis of clinical research in humans.[27] The primary outcome variable is a change on the VAS, where a difference of 10 mm is considered to be clinically meaningful.

Concentrations of gut hormones, glucose, and insulin are expressed as change from baseline and were compared using area under the curve (AUC), calculated using the trapezoidal rule. Change from baseline AUC for the blood parameters and ad libitum food intake were compared among treatments using a mixed effects linear model with a random subject effect (Proc Mixed). This procedure calculated treatment means, standard error, and statistical differences among means. Carry-over and interaction terms were tested in each model but were dropped from the final models because they were not significant. Data are presented as the mean ± SEM. Spearman correlation coefficient tests were performed to determine relationships between selected variables. Statistical significance was achieved at $p < 0.05$. All analyses were completed with SAS 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Subject Characteristics. Twenty subjects (10 men and 10 women) participated in this study. All 20 subjects completed all 5 study visits. The mean BMI was 23 ± 2 kg/m^2, and the mean age was 29 ± 8 years. Fasting values for glucose, insulin, GLP-1, and ghrelin did not differ among treatments.

Satiety-Related Questions. AUC hunger, satisfaction, and fullness were not different among fiber treatments. AUC prospective food intake did not differ for any of the fiber treatments compared to control, but SCF+P differed from SCF: subjects felt they could eat more following the SCF+P treatment than after the SCF treatment (Figure 1).

Food Intake. Energy intake at the lunch buffet and for the remainder of the day as reported by food records did not differ among treatments (Figure 2). There were also no differences in grams of carbohydrate, fat, protein, or fiber consumed during the postintervention period (data not shown).

Glucose and Insulin. The postprandial glucose and insulin response curves are displayed in Figure 3. The RS and RS+P treatments resulted in significantly reduced AUC glucose

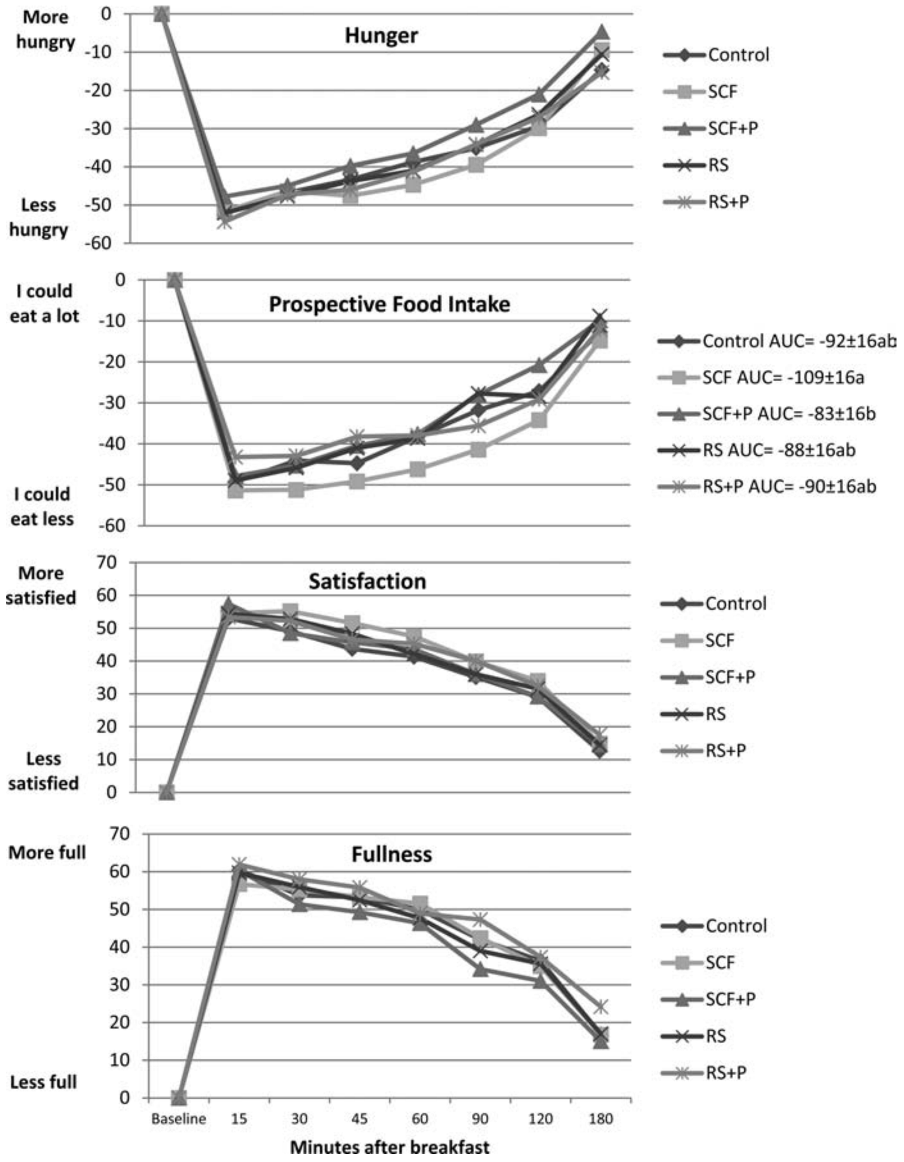

Figure 1. AUC for satiety-related questions, expressed as change from baseline. For prospective food intake, the numbers following the fiber treatment in the legend represent AUC score ± SEM. Treatments with different letters have statistically different AUC ($p < 0.05$). AUC scores are not shown if there were no significant differences among treatments. P, pullulan; RS, resistant starch; SCF, soluble corn fiber.

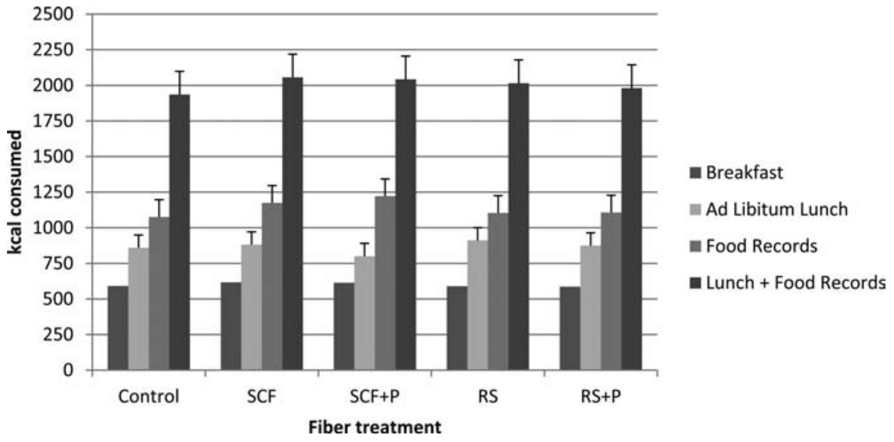

Figure 2. Calorie intake (mean ± SEM) throughout the day of the intervention. There were no significant differences in calories consumed at the lunch buffet or the remainder of the day as reported by food records. Total intake after breakfast (lunch plus food records) was also not different. P, pullulan; RS, resistant starch; SCF, soluble corn fiber.

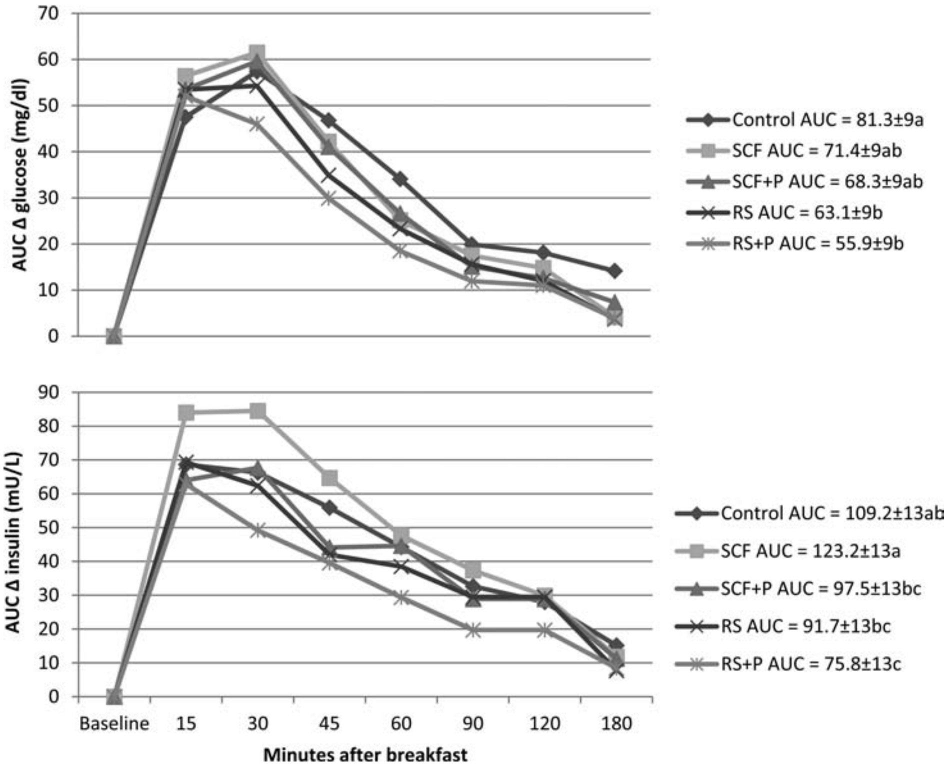

Figure 3. AUC glucose (top) and insulin (bottom), expressed as change from baseline. The numbers after each treatment represent the AUC ± SEM. Treatments with different letters have statistically different AUC ($p < 0.05$). P, pullulan; RS, resistant starch; SCF, soluble corn fiber.

compared to control. The glucose response following the SCF and SCF+P treatments did not differ from control or the RS treatments. AUC insulin was significantly reduced following the RS+P treatment compared to control. SCF resulted in significantly higher AUC insulin compared to SCF+P and the RS treatments. Glucose and insulin did not correlate with any of the subjective appetite measures, but there was an inverse relationship between AUC insulin and calories consumed at lunch and for the remainder of the day (Spearman $r = -0.37$, $p = 0.0003$).

Gut Hormones. AUC GLP-1 was significantly reduced following the RS+P treatment compared to control and the SCF treatments (Figure 4). AUC GLP-1 was significantly correlated with the subjective measures of appetite. Higher concentrations of GLP-1 were associated with greater fullness (Spearman $r = 0.30$, $p = 0.002$) and satisfaction (Spearman $r = 0.30$, $p = 0.002$) and lower hunger (Spearman $r = -0.25$, $p = 0.01$) and prospective food intake (Spearman $r = -0.24$, $p = 0.02$). AUC ghrelin did not differ among treatments (Figure 4) and did not correlate with any of the subjective appetite measures.

Breakfast Palatability. Ratings for visual appeal, smell, and aftertaste did not differ among treatments. Subjects rated the taste of both SCF breakfasts similar to the control and more favorably than both RS breakfasts (Figure 5). The taste of the RS+P breakfast was the least preferred and was also significantly lower than control. Rating for overall pleasantness followed a similar pattern: both SCF breakfasts were rated as significantly more pleasant than the control and both RS treatments. The RS+P treatment had lower overall pleasantness than control.

■ DISCUSSION

Novel dietary fibers are continuously being developed to increase fiber content in foods, but limited information is available regarding the physiological effects of these ingredients in humans.

Increased satiety is a commonly reported benefit of dietary fiber consumption. In the present study, despite providing high levels of fiber, there were no differences in any of the subjective appetite sensations or energy intake compared to the low-fiber control. Our results are consistent with data showing minimal impact of RS on satiety. de Roos et al. found that supplementation with 30 g/day type 2 (intrinsically resistant) RS or type 3 RS had little effect on appetite or energy intake compared to glucose.[28] Similarly, consumption of 48 g of type 2 RS divided over two meals had no effect on appetite ratings, but did reduce energy intake at an ad libitum evening meal.[29] Intake of two preloads containing 11.2 g of type 3 RS each had no effect on satiety or food intake compared to an isoenergetic, low-fiber control.[30] In contrast, Willis et al. reported increased satiety with consumption of 8 g of RS.[10] Some research suggests RS may have a delayed impact on satiety mediated by colonic fermentation and production of short-chain fatty acids.[31] The duration of our study may not have been long enough to capture the influence of these effects on appetite.

The effect of SCF on satiety has not been well studied. Supplementation of two carbohydrate beverage preloads with 11.8 g of SCF each had no effect on appetite ratings or energy intake at a subsequent lunch compared to an isoenergetic control.[30] The amount of fiber provided was similar to the current study and suggests that SCF has minimal effects on satiety when added to a carbohydrate beverage or a mixed meal.

Interestingly, we found that prospective food intake was greater (AUC was less negative) during the postprandial period following the SCF+P treatment compared to SCF. This effect may be related to differences in the insulin responses elicited by these treatments. AUC insulin was significantly higher after SCF compared to SCF+P and was negatively correlated with energy intake. A meta-analysis by Flint et al. found that postprandial

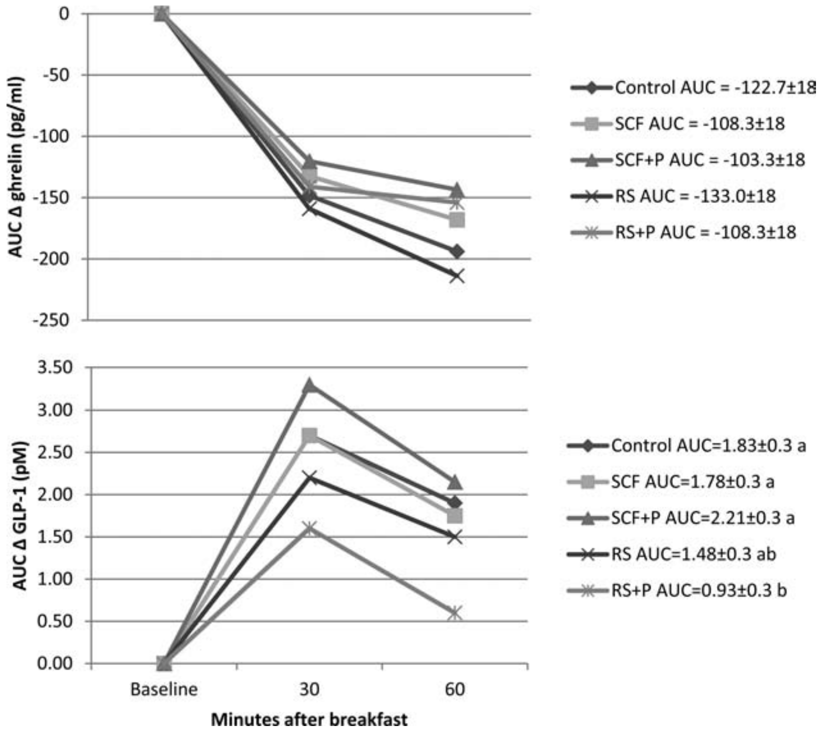

Figure 4. AUC ghrelin (top) and GLP-1 (bottom), expressed as change from baseline. The numbers after each treatment represent the AUC ± SEM. Treatments with different letters have statistically different AUC ($p < 0.05$). GLP-1, glucagon-like peptide-1; P, pullulan; RS, resistant starch; SCF, soluble corn fiber.

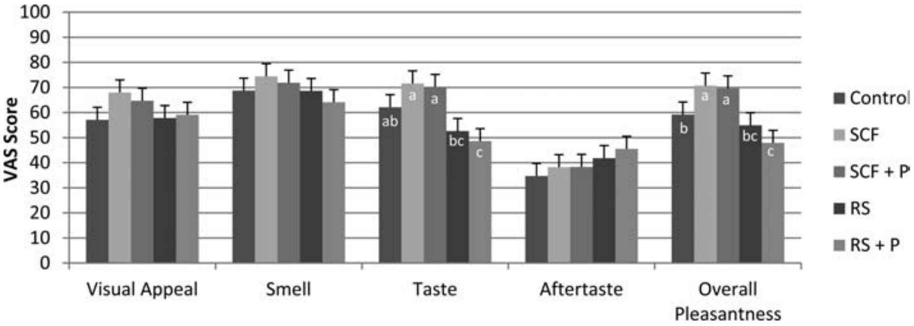

Figure 5. Palatability ratings (mean ± SEM) for the test breakfasts. A higher score indicates better visual appeal, smell, taste, overall pleasantness, and more aftertaste. Within a palatability category, treatments with different letters have statistically different palatability ratings ($p < 0.05$). P, pullulan; RS, resistant starch; SCF, soluble corn fiber; VAS, visual analog scale.

insulin was associated with increased satiety and decreased hunger and energy intake in normal-weight subjects.[32] Furthermore, there is evidence that insulin is a regulator of ghrelin suppression.[33−35] It is possible that higher insulin concentrations following SCF caused greater suppression of ghrelin over the postprandial period, and this may have altered appetite sensations. However, because ghrelin was only measured for 60 min after the test meal, we are unable to confirm that effect in this study. Additionally, despite lower insulin responses with the two RS treatments compared to SCF, there were no differences in appetite sensations. This indicates that additional factors are involved in the regulation of satiety and energy intake.

The reduction in glycemic response following the RS treatment is consistent with other studies reporting lower glycemic and/or insulinemic responses following acute or chronic intake of RS.[29,36,37] Addition of 5 g of pullulan to the RS treatment (RS+P) resulted in lower AUC for both glucose and insulin compared to control. Not surprisingly, Wolf et al. found that consumption of 50 g of pullulan, compared to digestible maltodextrin, resulted in 50% lower iAUC.[38] A reduction in postprandial glucose and insulin was also observed following consumption of a beverage containing 25 g of pullulan.[39] Although the doses used in these studies are higher than that used in the present study, this suggests that addition of pullulan to the RS meal contributed to the reduction in the glycemic and insulinemic response.

Alternatively, the SCF and SCF+P treatments did not alter the glucose or insulin response compared to the control meal. These results differ from a previous study in which subjects consumed 25 g of pullulan, SCF, RS, or a 50/50 blend of SCF and pullulan mixed with a lemonade beverage.[39] The incremental AUC for glucose and insulin was significantly lower for all fiber treatments compared to glucose. However, these meals were not matched for available carbohydrates, so these differences likely reflect the greater availability of digestible carbohydrate in the control treatment. Our results suggest that when provided as a mixed meal matched for macronutrient and available carbohydrate content, SCF does not reduce the glucose or insulin response to a meal. However, SCF may still be useful for attenuating postprandial glucose concentrations if used to lower the available carbohydrate content of a food product. Future studies should examine this application for SCF in a mixed meal, which may be more physiologically relevant than a carbohydrate beverage.

Modulation of gut hormones is a potential mechanism by which fiber might influence satiety, yet few studies evaluate gut hormone concentrations following a mixed meal containing fiber. We found that AUC GLP-1 following consumption of RS+P was significantly lower than GLP-1 concentrations following the low-fiber control. Others have also reported a suppressive effect of fiber on GLP-1.[40−42] These studies used viscous fibers, which may have delayed gastric emptying and nutrient absorption, resulting in fewer nutrients acting to stimulate GLP-1 release. Pullulan is a viscous fiber and therefore may have influenced GLP-1 release via this mechanism. This would also be consistent with the reduced glycemic response observed for the RS+P treatment in this study. However, to our knowledge, the effect of pullulan on gastric emptying has not been evaluated. In addition, a suppressive effect was not observed for SCF+P, so it is possible that both RS and P contribute to this effect. All other fiber treatments resulted in AUC GLP-1 values that were not different from control. These results are consistent with other studies finding no effect of fiber on postprandial GLP-1 concentrations.[36,43−45]

We also found that postprandial ghrelin concentrations were not different among treatments. Ghrelin decreases rapidly following nutrient intake, with the depth and duration of suppression related to caloric load and meal composition. In our study, ghrelin values were not yet returning to baseline at 60 min. Other studies have reported differences in ghrelin when measured for several hours after a test meal.[46,47] It is possible that the time frame of measurement in this study was too short to capture differences in duration of ghrelin suppression. In general, the results of this study do not support the hypothesis that fiber influences satiety via effects on gut hormones.

The SCF and SCF+P treatments were generally rated as more palatable than the RS and RS+P treatments. However, this did not correspond to differences in appetite ratings between these treatments. This is consistent with a review which found that palatability has an inconsistent effect on appetite following a test meal.[48] Our results indicate that SCF can be added to food products at high levels without negatively affecting taste and therefore may be useful for increasing fiber in the diet.

In conclusion, addition of 25 g of fiber to a meal had no effect on subjective appetite ratings or ad libitum energy intake in healthy volunteers. Postprandial serum parameters varied by fiber treatment. RS, alone or in combination with pullulan, significantly reduced glycemic response compared to control. In contrast, treatments containing SCF did not alter any serum parameters compared to control. Although not always significant, there appeared to be a trend for RS and RS+P to reduce AUC glucose, insulin, and GLP-1 compared to the SCF treatments. These findings warrant further research with larger sample size and greater statistical power to better understand the differing responses to these fiber sources. This further highlights the importance of evaluating the physiological effects of novel fibers in vivo to guide their use as functional ingredients in food products.

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Notes

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■ ABBREVIATIONS USED

AUC, area under the curve; BMI, body mass index; GCRC, general clinical research center; GLP-1, glucagon-like peptide-1; P, pullulan; RS, resistant starch; SCF, soluble corn fiber; VAS, visual analog scale.

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