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Influence of Cross-Linked Arabinoxylans on the Postprandial Blood Glucose Response in Rats

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ABSTRACT: Viscous dietary fibers are well established to reduce the blood glucose response to a meal. In this study, arabinoxylans, the most abundant dietary fiber in most cereals, were extracted under alkaline conditions and cross-linked by using laccase. Cross-linking of the arabinoxylans led to gel formation and increased in vitro viscosity almost 100-fold after drying and rehydration. To determine the ability of these cross-linked arabinoxylans to blunt the postprandial blood glucose curve of a meal, arabinoxylans, either native or cross-linked, and either prehydrated or not, were fed to rats as part of a meal, and blood glucose was monitored at intervals after the meal. Cellulose, a nonviscous fiber, served as a control. Cross-linked, but not native, arabinoxylans significantly reduced the area under the blood glucose time curve 5−9% relative to cellulose, indicating that they remained viscous within the gastrointestinal tract, and thus likely provide the health benefits found with other viscous fibers.

KEYWORDS: *glycemic response, dietary fiber, arabinoxylan, weak gels, ferulic acid*

INTRODUCTION

The prevalence of type 2 diabetes has dramatically increased throughout the world in the last 30 years,[1] resulting in large increases in mortality and morbidity related to type 2 diabetes, thus creating a major global health problem.[2] A dietary approach to reducing the incidence of type 2 diabetes that has received considerable attention is a reduction in the rates of digestion and absorption of carbohydrates, manifested as a reduction in the postprandial blood glucose concentration, and quantified as the glycemic index. It has been suggested that long-term consumption of high glycemic index foods may chronically increase insulin demand, which would promote insulin resistance and impair pancreatic β-cell function[3] that could, over time, lead to the development of type 2 diabetes. A number of epidemiological studies support an association between consumption of a high glycemic index diet and a greater incidence of type 2 diabetes,[4−9] whereas only a few have not found this association.[10,11] A meta-analysis has found a significant positive association between a high dietary glycemic index and type 2 diabetes incidence.[12] Thus, there is considerable support from epidemiological studies for the concept that a low glycemic index diet will reduce the risk of developing type 2 diabetes.

Soluble fibers that form viscous solutions have repeatedly been demonstrated to effectively reduce the postprandial blood glucose response.[13,14] Viscosity of a polysaccharide in solution is a function of its concentration and factors determining its hydrodynamic volume, that is, average molecular weight, molecular weight distribution, and conformation in solution. Arabinoxylans, which are the dominant fiber compounds of most cereal grains, are constituents of the cereal plant cell wall. Although a small portion of the arabinoxylans is extractable with water, the majority of arabinoxylans is only solubilized by using alkaline conditions. Water-extractable arabinoxylans from wheat were described to be semiflexible,[15] showing similarities to the conformation of galactomannans. The viscosity of arabinoxylan solutions can be dramatically enhanced by cross-linking the arabinoxylans[16] through ferulate dimers[17] or higher oligomers,[18,19] thus increasing the molecular weight. However, arabinoxylan cross-linking can also result in gels.[20,21] Gel formation is due to the development of a three-dimensional arabinoxylan network, which is able to trap large amounts of solvent. It has been shown that arabinoxylan consumption reduces the postprandial blood glucose response in healthy subjects.[22] As arabinoxylan cross-linking dramatically increases the viscosity of arabinoxylan solutions or even forms arabinoxylan gels, the effect of arabinoxylans on the reduction of the postprandial blood glucose levels can theoretically be increased by arabinoxylan cross-linking. Thus, the aim of this study was to determine the effect of consumption of cross-linked arabinoxylans on the postprandial blood-glucose level in an animal model. We report here that while native arabinoxylans had no effect on the postprandial blood glucose response, cross-linked arabinoxylans significantly reduced the blood glucose response, indicating that a relatively simple modification of arabinoxylans to increase their viscosity may provide an important health benefit.

MATERIALS AND METHODS

Chemicals. All chemicals used were of reagent grade and were purchased from Sigma-Aldrich (St. Louis, MO) or Fisher Scientific (Pittsburgh, PA) unless otherwise indicated.

Preparation of Destarched Corn Bran. Corn bran (*Zea mays* L.) was kindly provided by Cargill, Indianapolis, IN. Corn bran was milled (particle size <0.5 mm) and extracted three times for 2 h each with acetone (first extraction, 1.5 L/kg, second and third extraction, 0.5 L/

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kg). Defatted bran was dried overnight in a hood, followed by 4 days in a vacuum oven at 40 °C. Defatted bran (500 g) was suspended in sodium phosphate buffer (pH 6.0, 0.08 M, 2.6 L), and α-amylase (15 mL) (Termamyl 120 L, Type L; Novozymes, Franklinton, NC) was added. The suspension was heated for 1 h in a boiling water bath with occasional shaking. Destarched corn bran was recovered by filtration (filter paper, pore size 20−25 μm) and washed twice each with hot water (70 °C), 95% (v/v) ethanol, and acetone. Destarched bran was dried in a hood and a vacuum oven as described above.

Extraction of Arabinoxylans. Destarched bran (150 g) was suspended in 0.5 M NaOH (3 L) and stirred for 4 h. In preliminary studies to determine optimum conditions for gel formation, alkaline hydrolysis (extraction) was also performed for 9 h. The pH was adjusted to 4.0 by using 6 M HCl, and the residue was removed by filtration (filter paper, pore size 20−25 μm). The solubilized arabinoxylans were precipitated by adding ethanol (final ethanol concentration: 65% (v/v)). The precipitated arabinoxylans were separated by filtration (filter paper, pore size 20−25 μm; miracloth, pore size 22−25 μm) and washed with 80% (v/v) ethanol, absolute ethanol, and acetone. The arabinoxylans (and coextracted compounds) were suspended in acetone and treated for 10 min in an ultrasonic bath, followed by filtration and drying in a hood and a vacuum oven.

Preparation of Arabinoxylan Gels. Gels for the animal study were prepared by dissolving the dried arabinoxylans (5 g) in a citric acid/phosphate buffer (0.05 M, pH 5.5, 125 mL). The beaker was placed in a heated water bath (40 °C), and, after temperature adjustment, laccase (from *Trametes versicolor*; Fluka, Steinheim, Germany) (12.5 mL, 0.04 U/μL citric acid/phosphate buffer) was added. The gel was allowed to set for 2 h before being freeze-dried. The dry powder was pulverized by using mortar and pestle. The freeze-dried powder contained 5 g of arabinoxylans (and coextracted compounds) and 3.5 g of buffer salts.

In preceding studies, we optimized the gelation conditions for the needs of the animal study. To determine gel strengths of differently concentrated gels prepared at different temperatures (room temperature, 40 °C, 50 °C), 1%, 2%, 3%, and 4% gels were prepared as described. However, the amounts of arabinoxylans dissolved in 5 mL of buffer as well as the volumes of added laccase solutions were adjusted according to the desired gel concentration. The gels were prepared in 10 mL beakers and directly used to measure the gels strengths as described below. To determine the gel strengths of the gels after freeze-drying and rehydrating, the freeze-dried gels were pulverized, dissolved/suspended in 5 mL of water in 10 mL beakers, and used for gel hardness determinations.

Gel Hardness Determination. Hardness (strength) of the freshly prepared gels was determined by using a texture analyzer TA.XTplus (Stable Micro Systems, Surrey, UK). A cylindrical plunger (TA 10, 1.3 cm diameter) was driven into the gel for 4 mm by using a constant speed of 1.0 mm/s. The peak height at a compression of 4 mm was defined as gel hardness.[23]

Viscosity Determination Using a Rapid Visco Analyzer. The viscosities of 3% solutions/suspensions of the extracted arabinoxylans, the arabinoxylan gels prepared for the animal study, hydroxypropyl methylcellulose (HPMC) (K4M, K15M, Methocel, Dow Chemical Co., Midland, MI), and cellulose (Dyets Inc., Bethlehem, PA) were determined by using a Rapid Visco Analyzer. The sample (0.75 g) was added to water (25 mL) in a disposable sample container, the paddle was added, and both were inserted into the Rapid Visco Analyzer. The temperature was held constant at 37 °C. The paddle speed was set for 30 min at 950 rpm. After 30 min, the speed was lowered to 160 rpm, and the viscosity was measured as the torque required to maintain the paddle's speed at a constant 160 rpm.

Carbohydrate Composition of the Extracted Arabinoxylans. Neutral sugars were released by acidic hydrolysis as described by Englyst et al.[24] with minor modifications (12 M H_2SO_4 for 5 min at 35 °C, 2 M H_2SO_4 for 120 min at 100 °C) and analyzed as their alditol acetates[25] by GC-FID (GC Focus Series, Thermo Electron S.p.A., Milan, Italy) on a DB-225 capillary column (30 m × 0.25 mm i.d., 0.15 μm film thickness) (Agilent Technologies, Santa Clara, CA). Chromatographic conditions: initial column temperature was 180 °C, held for 5 min, ramped at 1 °C/min to 186 °C, ramped at 4 °C/min to 210 °C, held for 8 min, ramped at 10 °C/min to 220 °C, held for 2 min; split injection (split ratio 1/25, injector temperature 225 °C); flame ionization detection (detector temperature 250 °C). Helium (3 mL/min) was used as carrier gas.

Animals. Male Wistar rats (Harlan Laboratories, Indianapolis, IN) were housed individually in stainless steel mesh cages in a temperature-controlled room (22−23 °C) with a 12 h light−dark cycle. The initial weight of the animals was between 150 and 175 g. Rats were given free access to food and water. Animal handling and housing followed National Institutes of Health guidelines, and experimental procedures were approved by the University of Minnesota Animal Care and Use Committee.

Diets. Rats were adapted to a standard rodent powdered diet (AIN-93G) (basal diet) prior to the start of the study. The compositions of the test diets were as follows (per kg): 347.5 g of corn starch, 200 g of casein, 150 g of soy oil, 115 g of dextrins, 87 g of sucrose, 35 g of mineral mix, 10 g of cellulose, 10 g of vitamin mix, 3 g of L-cysteine, 2.5 g of choline bitartrate, 40 g of test dietary fibers. In addition, 0.014 g of butylated hydroxytoluene was added to each diet to prevent oxidation of the fat.

A preliminary study was conducted to examine the influence of the intestinal milieu on the hydrated structure of the dietary fibers and determine how they were affected by centrifugation of the intestinal contents. Animals fasted overnight were meal-fed 4 g of their respective diets, as described below, and, 2 h after the meal, anesthetized by inhalation of isoflurane. The animals were opened by a midline incision, the small intestine removed, the intestinal contents collected by finger stripping, and the contents centrifuged at 30 000*g*, as previously described.[26]

Animals were randomly divided into six treatment groups with eight animals per group. The test dietary fibers were cellulose as a negative control, HPMC (K4M and K15 M in a 50/50 (w/w) ratio) as a positive (medium/high viscosity) control, extracted arabinoxylans in the dry state, prehydrated extracted arabinoxylans, cross-linked arabinoxylans in the dry state, and prehydrated cross-linked arabinoxylans. As complete hydration is necessary to obtain full viscosity, and hydration can be a lengthy process, we chose to test whether prehydration of the arabinoxylans influenced the postprandial blood glucose levels. The prehydrated fiber sources were prepared by swelling in water, using a ratio of 20 mL/g of arabinoxylans and 30 mL/g of cross-linked arabinoxylans, before addition to the basal diet. Thus, the added fiber sources composed 4% of the test diets. Because the basal diet contained 1% fiber as cellulose, the total dietary fiber content for each test diet was 5%.

Animal Study Design. The night prior to the study, the rats were deprived of food for 8 h. The following morning, rats were weighed, their tails were disinfected with isopropanol−water (63/37 (v/v)), a small amount of venous blood was taken, and the blood glucose concentration was measured by using the Ascensia Contour Blood Glucose Monitoring meter (Bayer Healthcare LLC, Tarrytown, New York) equipped with blood glucose strips 7090 G. Preliminary studies indicated that a meal size of 4 g resulted in differences in the consumed amounts of feed. Therefore, the meal size was reduced to 2.5 g. Thus, exactly 2.5 g of the test diet (described above) was then presented to the animal in a standard feed cup as a single meal, which was entirely consumed within 15 min of presentation. Thus, each test meal contained 1.32 g of digestible carbohydrate. Blood glucose concentrations were determined 30, 60, 120, 180, and 240 min after meal presentation, as described above. Blood glucose determination was performed in duplicate at each time point unless measured concentrations differed more than 10 mg/dL. In this case, a third measurement was performed, and only the two values differing less than 10 mg/dL were used.

Data Analysis. Analysis of variance was conducted to determine the effect of dietary fiber on blood glucose concentrations, using the SAS System for Windows, release 9.1 (SAS Institute, Cary, NC). Differences among individual fiber treatments were inspected using Duncan's multiple range test. Two-way analysis of variance was carried

out on the arabinoxylan groups to examine the main effects of cross-linking and prehydration.

RESULTS AND DISCUSSION

Arabinoxylan Extraction, Cross-Linking, and Characterization. Arabinoxylans were extracted from destarched corn bran by using 0.5 M NaOH. Solubilized arabinoxylans were subsequently precipitated in ethanol as previously described by Carvajal-Millan and co-workers.[27] Alkaline extraction for 9 h resulted in only slightly higher yields than 4 h extraction (24% vs 22%). Viscosities of 1%, 2%, 3%, and 4% solutions of the extracted arabinoxylans logically increased with increasing arabinoxylan concentrations, but were comparable for both 4 h- and 9 h-extracted arabinoxylans (data not shown). The extracted arabinoxylans were cross-linked by using laccase and oxygen. The pH of this reaction was kept constant at 5.5; variable parameters included arabinoxylan concentration and temperature. Whereas cross-linking of 1% arabinoxylan solutions led to medium (if cross-linked at room temperature or at 50 °C) to highly (if cross-linked at 40 °C) viscous solutions, gels were formed by cross-linking 2−4% arabinoxylan solutions. Gel strengths increased with enhanced arabinoxylan concentrations used for gel preparation as shown in Figure 1

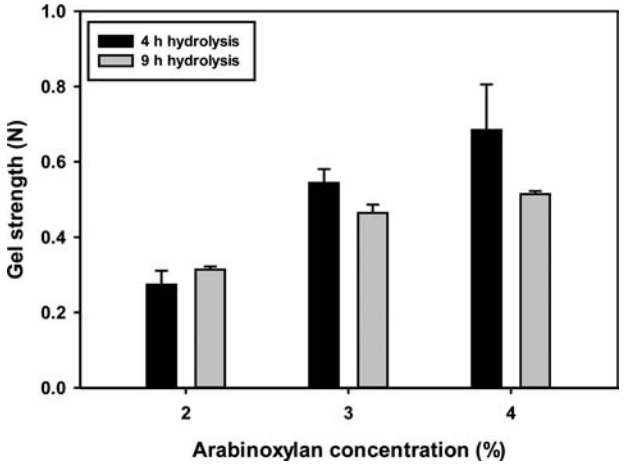

Figure 1. Strengths of arabinoxylan gels prepared from differently concentrated arabinoxylan solutions by applying laccase at room temperature. Arabinoxylans obtained from 4 and 9 h alkaline extractions (hydrolyses) were used.

for gels formed at room temperature. Also, arabinoxylans from 4 h extractions formed slightly harder gels as compared to arabinoxylans obtained by a 9 h alkaline extraction procedure (3% and 4% solutions). If used as a functional food ingredient, cross-linked arabinoxylans would likely be incorporated into food products in their dry state. Thus, the gels were freeze-dried, rehydrated, and the viscosities/gel strengths of the rehydrated cross-linked arabinoxylans were assessed. The rehydrated arabinoxylans still formed viscous solutions or weak gels. Determination of the gel strengths of the 4% gels by using the texture analyzer was, however, difficult, resulting in high variability. Trends suggested that a temperature of 40 °C during cross-linking led to slightly stronger rehydrated gels than cross-linking at either room temperature or 50 °C. Just as observed for the freshly prepared gels, the rehydrated gels prepared from arabinoxylans from 4 h extractions were slightly stronger than those prepared from arabinoxylans from 9 h extractions.

According to the results of these in vitro studies, arabinoxylans for the animal studies were prepared by a 4 h alkaline extraction procedure. The carbohydrate composition of the extracted arabinoxylans was arabinose/xylose/galactose/glucose 31/61/7/2 (molar basis). Mannose, rhamnose, and fucose were not detected or were detected in trace amounts only. The arabinose/xylose ratio was 0.51, slightly lower than those for other alkaline corn bran extracts,[27−29] indicating a moderately branched structure. While the likely origin of galactose is from arabinoxylan side-chains,[29,30] the small amounts of glucose presumably stem from contaminating glucans, that is, starch remnants after α-amylase treatment. These arabinoxylans were cross-linked by using a 4% arabinoxylan solution and a temperature of 40 °C. The gels were freeze-dried prior to use in the animal study.

The viscosities of these fiber sources and of the controls (HPMC as positive control, cellulose as negative control) (all fibers 3% in water) were analyzed in a Rapid Visco Analyzer. While insoluble cellulose logically showed no and the extracted arabinoxylans showed only weak viscosity (ca. 40 cP), the viscosities of the hydroxypropyl methylcellulose (ca. 4500 cP) and the cross-linked arabinoxylans (ca. 3900 cP) were noticeably higher. However, HPMC forms viscous solutions, whereas rehydrated cross-linked arabinoxylans lead to the formation of weak gel-like structures. The rehydrated, cross-linked arabinoxylans do not support their own weight, which would initially suggest a viscous solution; however, centrifugation removes all viscosity, thus indicating a weak gel-like structure (centrifugation leads to a breakdown of the gel-like structure) rather than a viscous solution.

Animal Study. The cellulose negative control showed a rapid, steep increase in blood glucose levels after the meal, followed quickly by a decline (Figure 2). However, the baseline was not reached within 4 h after the intervention, just as in the other groups. HPMC, which has been demonstrated to raise the viscosity of intestinal contents,[31,32] and to blunt the postprandial glucose curve,[33] was used as a positive control. In contrast to the cellulose group, the HPMC group of the blood glucose levels peaked at a lower concentration than the cellulose group and then plateaued for 2 h before decreasing. However, the blood glucose levels for both the cellulose and the HPMC groups after 180 min were comparable (127 vs 128 mg/dL). Thus, the negative and positive controls showed the expected results on the blood glucose levels, with HPMC blunting the blood glucose response.

Table 1 shows the total area under the time curve (AUC) for blood glucose, the maximum blood glucose concentration (C_{max}), and the time at which the maximum blood glucose concentration occurred (T_{max}) for each diet group. The total AUC for the HPMC, cross-linked arabinoxylans, and prehydrated, cross-linked arabinoxylans groups was significantly less than the cellulose group. The total AUC for the arabinoxylan and prehydrated arabinoxylan groups did not differ from the cellulose group. The C_{max} values for both arabinoxylan samples (not prehydrated and prehydrated) were 141 and 151 mg/dL, respectively, and were not significantly different. Thus, the C_{max} for the arabinoxylans group fell between the values for C_{max} for our positive and negative controls, whereas the C_{max} for the prehydrated arabinoxylans group was essentially the same as the cellulose negative control group. Cross-linking of the arabinoxylans led to a C_{max} of 135 and 133 mg/dL for the not prehydrated and prehydrated samples, respectively, demonstrating that cross-linked arabinox-

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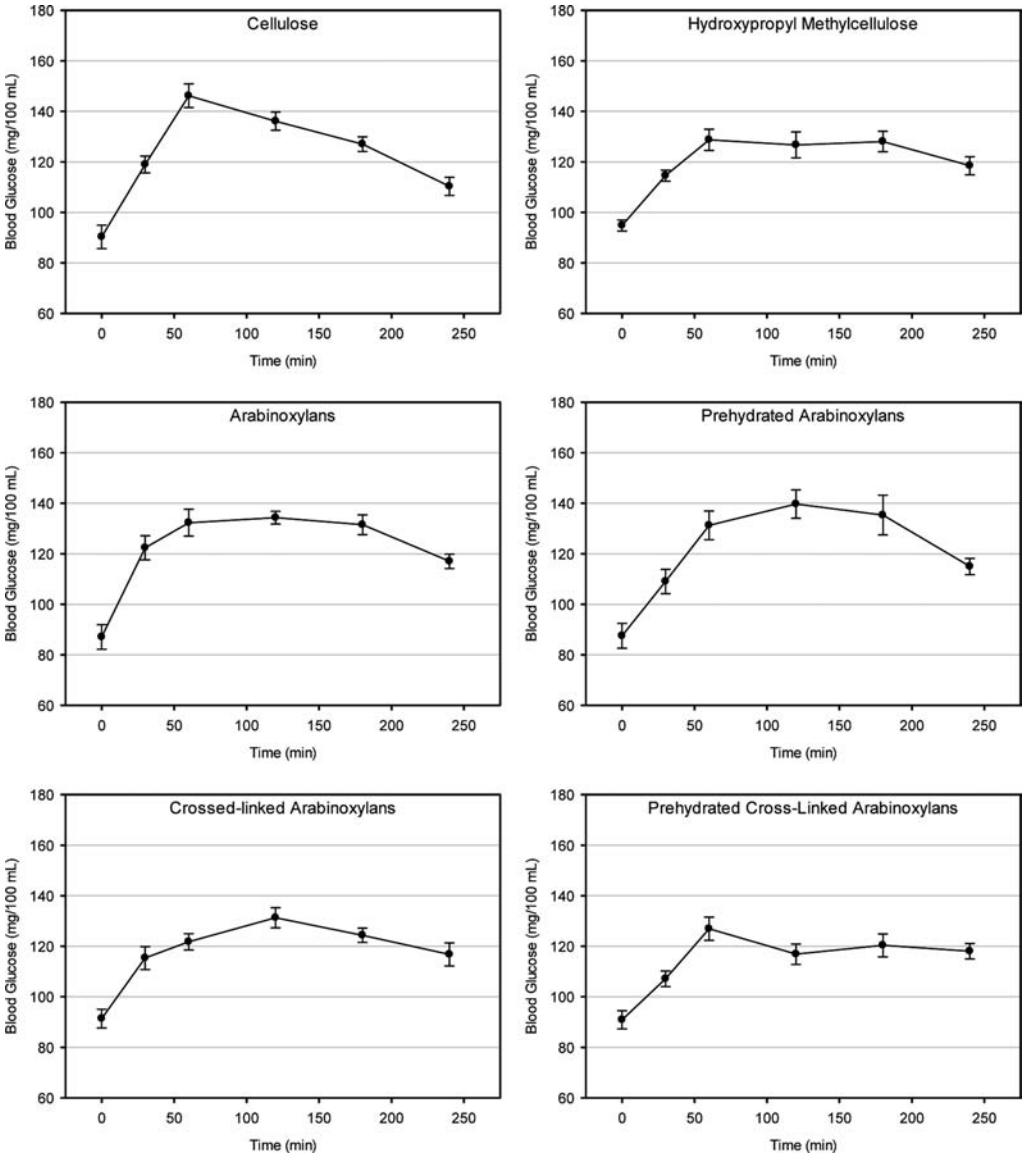

Figure 2. Blood glucose concentrations over time after a meal containing cellulose, hydroxypropyl methylcellulose, native arabinoxylan, or cross-linked arabinoxylan. Both native and cross-linked arabinoxylan were fed either dry or prehydrated. Values represent mean ± SEM, n = 8.

Table 1. Total Area under the Time Curve (AUC), Maximal Glucose Concentration (C_{max}), and Time at Maximal Glucose Concentration (T_{max})[a]

	cellulose	HPMC	arabinoxylans	prehydrated arabinoxylans	cross-linked arabinoxylans	prehydrated and cross-linked arabinoxylans	significant main effects[b]
total AUC (mg·min/mL)	30 604 ± 488 a	29 496 ± 615 bc	30 392 ± 587 ab	30 441 ± 726 abc	29 159 ± 538 bc	28 066 ± 553 c	cross-linking (p = 0.006)
C_{max} (mg/dL)	150 ± 3 a	137 ± 4 b	141 ± 3 ab	151 ± 6 a	135 ± 4 b	133 ± 3 b	cross-linking (p = 0.010)
T_{max} (min)	78.8 ± 9.7	127.5 ± 17.7	101.3 ± 20.4	127.5 ± 13.6	116.3 ± 21.5	135 ± 29	none

[a]Values represent mean ± SEM, n = 8. Values not sharing a common superscript letter within a row are significantly different (p < 0.05). [b]Main effects analyzed were prehydration and cross-linking of arabinoxylans by two-way analysis of variance.

ylans can decrease the blood glucose maximum to a level comparable to the HPMC positive control. Although there was a trend for the T_{max} values to be greater in the HPMC, prehydrated arabinoxylans, and prehydrated, cross-linked arabinoxylans groups as compared to the cellulose group, there were no significant differences among the groups. Correlations between the logarithms of in vitro viscosities of the fiber sources, determined using the Rapid Visco Analyzer, and the means of the total AUC and C_{max} were calculated, setting the viscosity of cellulose arbitrarily to 1. For both measures of the blood glucose response, the correlations were very high (R^2 = 0.89 and p = 0.054 for total AUC; R^2 = 0.94 and p = 0.031 for C_{max}).

Two-way analysis of variance of the arabinoxylan groups indicated that cross-linking, but not prehydration, was a statistically significant main effect for both total AUC (p = 0.006) and for C_{max} (p = 0.010). That is, cross-linking of arabinoxylans significantly blunted the blood glucose response after a meal, as compared to arabinoxylans that were not cross-linked. However, prehydration of arabinoxylans before feeding had no effect on the blood glucose response relative to arabinoxylans that were not prehydrated.

Our finding that native arabinoxylans did not blunt the postprandial blood glucose response to a meal is in contrast to the findings of others. Normal subjects fed a single meal of bread containing arabinoxylan fiber had a lower incremental area under the curve for plasma glucose, as compared to control bread with no added arabinoxylan.[22] Bread containing 12 g of arabinoxylan had a greater lowering effect than the bread containing 6 g. The arabinoxylan concentration in the bread containing 6 g of arabinoxylan was similar to the concentration of arabinoxylans used in the present study (about 4% in both cases). However, because the in vitro viscosity of the native arabinoxylans used in the present study was quite low, it would not be expected to lower the blood glucose response in our study. However, our finding that cross-linking of arabinoxylans, which greatly increased its viscosity, resulted in a blunted postprandial glucose response is consistent with the concept that viscosity is the characteristic of dietary fiber responsible for the blunting response.

Although HPMC and cross-linked arabinoxylans both have a substantial viscosity in vitro, as analyzed by the Rapid Visco Analyzer, it is clear that they differ fundamentally in their hydrated structure. HPMC forms a true viscous solution, whereas cross-linked arabinoxylans form (weak) gels. This difference was confirmed in a preliminary study by examining the intestinal contents of rats fed either HPMC- or cross-linked arabinoxylans-containing diets. During collection of these intestinal contents, by observation it was clear that both sets of contents were highly viscous as compared to animals fed the cellulose-based diet. However, after centrifugation of the contents at 30 000g, the supernatant of the cross-linked arabinoxylan-containing intestinal contents had no viscosity, indicating that the gel structure had collapsed, whereas the supernatant from animals fed HPMC was highly viscous.

However, within the gastrointestinal tract, both structures appeared to slow glucose absorption. The mechanism by which viscous fibers slow glucose absorption remains uncertain, with evidence suggesting delayed gastric emptying,[34] slowed small intestinal transit,[35] or a reduced rate of glucose diffusion to the absorptive surface.[36] It is not known whether viscous materials such as HPMC or gels such as the cross-linked arabinoxylans act by different mechanisms. In the only study comparing the effect of a fiber-free meal to meals containing either a viscous material (guar gum) or to gels (alginates) on gastric emptying, no differences in gastric emptying were found among any of the treatments.[37] Thus, the mechanism by which the cross-linked arabinoxylans blunt the postprandial glucose concentration remains uncertain.

In conclusion, we extracted and cross-linked arabinoxylans from corn bran to produce a material with gel-like characteristics and high viscosity in vitro. When fed to rats as part of a meal, these cross-linked arabinoxylans blunt the postprandial blood glucose concentration, as compared to a nonviscous dietary fiber, indicating that the cross-linked arabinoxylans maintain their viscosity within the gastrointestinal tract. Given that viscous dietary fibers are also well-known to lower plasma cholesterol concentrations, cross-linked arabinoxylans may be useful as a food component to provide several important health benefits. Further, as rehydration had no effect on whether the cross-linked arabinoxylans blunted the postprandial glucose response, they should be effective in foods regardless of the water content of the food.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

AUC, area under the postprandial blood glucose concentration curve; C_{max}, maximum blood glucose concentration; T_{max}, time of maximum blood glucose concentration; HPMC, hydroxypropyl methylcellulose

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