Whole-Grain Processing and Glycemic Control in Type 2 Diabetes: A Randomized Crossover Trial

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OBJECTIVE

To consider the effects of whole-grain processing, specifically milling, on glycemic control in free-living adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Participants of this crossover trial were randomized to two interventions of 2 weeks, separated by washout. They were advised to replace the grain foods they normally consumed with intervention foods. Intervention foods were nutrient-matched whole-grain products of wheat, oats, and brown rice that differed in their degree of processing. No other lifestyle advice was given. Continuous glucose monitoring systems were worn. Other cardiometabolic risk factors and alkylresorcinols (a biomarker of whole-grain intake) were measured pre- and postintervention.

RESULTS

Thirty-one adults with type 2 diabetes (63 ± 13 years old, BMI 32.4 ± 7 kg/m^2, HbA_{1c} 7.5 ± 3.4% [59 ± 14 mmol/mol]) commenced the trial; 28 (90%) completed both interventions. The increase in alkylresorcinols did not differ between interventions, and there was no difference in reported energy intake. Postprandial responses were 9% (95% CI 3–15) lower following breakfast and 6% (1–10) lower following all meals of less-processed whole grains when compared with finely milled grains. Day-long glycemic variability also was reduced when measured by 24-h SD (−0.16 mmol/L [95% CI −0.25 to −0.06]) and mean amplitude of glycemic excursion (−0.36 [95% CI −0.65 to −0.08]). Mean change in body weight differed by 0.81 kg (95% CI 0.62–1.05) between interventions, increasing during the finely milled intervention and decreasing during the less-processed whole-grain intervention. This was not a mediating factor for the glycemic variables considered.

CONCLUSIONS

Consuming less-processed whole-grain foods over 2 weeks improved measures of glycemia in free-living adults with type 2 diabetes compared with an equivalent amount of whole-grain foods that were finely milled. Dietary advice should promote the consumption of minimally processed whole grains.

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Diets rich in whole grains are associated with reduced incidence of type 2 diabetes, coronary heart disease, and colorectal cancer (1). Randomized controlled trials of increasing whole-grain intakes have demonstrated their potential to improve glycemic control, body weight, the lipid profile, and other cardiometabolic risk factors in adults with diabetes (2). Furthermore, their production has a lesser adverse effect on planetary health than is the case for many other nutrient-rich foods (3). Unsurprisingly, many national dietary guidelines (4) and recommendations for the management of diabetes (5,6) encourage whole-grain consumption and suggest replacing refined grains with whole grains.

Current definitions of the term whole grain permit the inclusion of highly processed and reconstituted fractions of whole grains (7,8). Furthermore, such finely ground products may be added into ultraprocessed foods, the consumption of which can lead to increased calorie intake and weight gain (9). There is evidence that the acute glycemic response to whole-grain foods is greater when grains have been finely milled (10). More recently, we have shown that the glycemic response to four different whole-grain wheat breads is related to the degree of grain processing in adults with type 2 diabetes (11).

To date, all relevant studies have examined the acute effects of whole-grain processing on postprandial glycemia in controlled settings. We have undertaken a 2-week randomized crossover trial in free-living adults with type 2 diabetes to determine whether the structural integrity of whole grains as a result of differences in milling is a determinant of overall glycemic control. We provided participants with their whole-grain foods and used continuous glucose monitoring (CGM) systems to assess glycemic control.

RESEARCH DESIGN AND METHODS

This randomized crossover trial compared two dietary interventions, each of 2-week duration, separated by a washout period of at least 2 weeks. The trial was conducted between October 2018 and April 2019 in Dunedin, New Zealand. The trial protocol was reviewed and approved by the Health and Disability Ethics Committee of the Ministry of Health, New Zealand (reference 18/STH/172). All participants provided written informed consent. The trial protocol was prospectively registered with the Australia New Zealand Clinical Trials Registry.

Participant Eligibility Criteria

Adults diagnosed with type 2 diabetes and aged between 18 and 80 years were eligible. Presence of comorbidities did not exclude participation; however, pregnancy, lactation, or a change in medication potentially influencing blood glucose control in the past 3 months did. Participants were recruited locally through general practices, fliers in supermarkets, online advertisements, and participation in earlier studies.

Randomization and Masking

The intervention order was determined by a computer-generated 1:1 block randomization protocol. Each intervention order was stored in a separate opaque envelope and accessed sequentially once each participant provided written consent. Participants were blinded to CGM data during both interventions and did not receive study feedback until both interventions were complete. The author who ran the analysis was blinded to the interventions for the initial comparisons. Given the nature of the interventions, participants could not be masked. They were aware of the research question this trial sought to address, and there were visible differences in the foods provided.

Interventions

Given that the aim of the trial was to examine the effect of food processing of whole grains on glycemic control and other cardiometabolic risk factors, we provided participants with commonly consumed whole-grain foods that differed in the extent of their milling. In one intervention, participants were provided with intact oats, brown rice, and whole-grain bread made with coarsely ground flour and kibbled wheat kernels. They were instructed to replace their current grain intake, determined by a preintervention 4-day diet record, with the foods provided. In the other intervention, participants were provided with instant oats, brown rice pasta, and whole-grain bread made with finely milled flour, and the same instructions to replace their current grain intake with the foods provided. No advice was given to change the amount of grains consumed. No further dietary or other lifestyle advice was given. Whole-grain foods were commercially available, were 100% whole grain (7,8), were matched for macronutrients and fiber, and met the American Association of Cereal Chemists International characterization of a whole-grain product (12).

Before the first intervention, participants completed a 4-day semiquantitative food diary to estimate their usual intakes. Metric cups were provided to each participant for use when weighing scales were not available. Participants attended the clinic on days 1, 7, and 14 during both interventions. On day 1, a baseline fasting blood sample and anthropometric measurements were taken, the intervention was explained, and participants received their whole-grain foods. CGM systems were fitted to the upper arm and activated. Participants were provided with daily checklists to record when and what intervention foods were consumed. On day 7, participants were provided with more intervention foods if required and given a 4-day semiquantitative food diary with instructions to capture 3 weekdays and 1 weekend day in the coming week. On day 14, the intervention ended, a fasting blood sample and anthropometric measurements were taken, and the CGM system removed.

Measurements

Anthropometric measurements (height, weight, and body composition) were recorded in duplicate, and resting blood pressure was measured three times. Participants wore a CGM system (FreeStyle Libre Pro; Abbot Laboratories) to measure interstitial glucose every 15 min for the duration of the interventions. This model was blinded so that data could not be viewed during the intervention. This model was also factory calibrated and did not need additional calibration against capillary blood measures. Fasting plasma samples were collected and stored at −80°C until analysis. Glycated hemoglobin A_{1c} (HbA_{1c}), cholesterol (total, LDL, and HDL), triglycerides, C-reactive protein, and α-1-acid glycoprotein were measured on an automated analyzer (Roche Diagnostics) after calibration with the appropriate standards. Fasting insulin was measured with a Bio-Plex magnetic bead array (Bio-Rad Laboratories), with concentrations calculated on standard curve data using the manufacturer's software. Alkylresorcinols

were measured as an objective marker of whole-grain intake (13).

Alkylresorcinol homologs C17:0, C19:0, and C21:0 were measured with liquid chromatography-high-resolution mass spectrometry (14) and then summed. Grain particle size for each of the foods provided in the interventions was characterized by sieve analysis (15), using 12 sieves from 63 to 5,600 μm.

The primary outcome investigated was a change in blood glucose control following meals and over the day. Postprandial glycemia was measured by the blood glucose incremental area under the curve (iAUC) with CGM data in the 3 h after breakfast, lunch, and dinner. Participants' food diary and habitual mealtimes provided the initial basis for identifying breakfast, lunch, and dinner time frames through a hierarchical decision-making process. Where the time of meal commencement could not be established, the data were excluded from the analysis. iAUC calculations for the 2-week interventions were based on 730 breakfasts, 734 lunches, and 764 dinners. Day-long variables were time spent in range (3.9–10.0 mmol/L), time spent below range (<3.9 mmol/L), time spent above range (>10.0 mmol/L) (16), and measures of glycemic variability. The daily measures of glycemic variability were the SD of the mean (16), the continuous overall net glycemic action (17), and the mean amplitude of glycemic excursion (MAGE) (18). Values of glycemic variability were calculated (19). Nutrition information was obtained from manufacturers. Dietary data were analyzed with FoodWorks 9 (Xyris Software) using the New Zealand FOODfiles 2016, supplemented by AusFoods 2017.

Statistical Analysis

The sample size estimate was based on a power calculation with an α of 0.05 and power of 0.80 to detect within-group differences in primary outcome variables, a 20% difference in mean postprandial glycemia as measured by iAUC. Twenty-eight participants were required to complete both interventions. Data were analyzed according to intention to treat. Analyses of CGM data were performed with a mixed model accounting for intervention order. An interaction between each glycemic variable and weight change during the intervention period was considered. For pre- and postintervention measures, we compared the difference in one intervention with the difference in the other intervention. The data for CGM variables, triglycerides, HDL cholesterol, alkylresorcinols, and markers of inflammation were log-transformed to address skew. Analyses were performed using Stata 15 (StataCorp, College Station, TX). Results are mean ± SD unless otherwise stated.

RESULTS

The flow of participants through the trial is shown in Fig. 1. Of the 31 participants with type 2 diabetes randomized, 28 (90%) completed both interventions. Fourteen (45%) of the 31 participants were female. Mean age was 63 ± 13 years. Mean HbA_{1c} was 7.5 ± 3.4% (59 ± 14 mmol/mol), and mean diabetes duration was 11.4 ± 9 years. Participants self-identified as being of New Zealand European (n = 25, 81%), Māori (n = 3, 10%), European (n = 2, 6%), or Indian (n = 1, 3%) ethnicity. The majority of participants were on oral hypoglycemic agents metformin and/or gliclazide (n = 19, 61%), with nine (29%) on both oral hypoglycemic agents and insulin and three (10%) able to control their blood glucose with diet alone. Three (10%) participants were current smokers.

Characteristics of the intervention foods are shown in Table 1, with full details of the sieve analysis available in the Supplementary Material. Dietary intakes before and during the interventions are shown in Table 2. During both intervention periods, total carbohydrate, starch, and dietary fiber increased at the expense of fat intake compared with baseline levels. Intakes of all macronutrients and dietary fiber were comparable between the two interventions. The increase in alkylresorcinols during the less-processed whole-grain intervention (from 55.8 ± 63 to 141.2 ± 295 nmol/L) was comparable (P = 0.403) with the increase during the intervention of finely milled whole grains (from 49.5 ± 41 to 171.9 ± 336 nmol/L). During the interventions, participants consumed a mean intake of 5.5 ± 1.3 servings of less-processed whole grains or 5.5 ± 1.4 servings of finely milled whole grains each day. The most servings of whole grains were consumed at breakfast (2.3 ± 0.9 and 2.2 ± 0.9) and then at lunch (1.8 ± 0.8 and 1.8 ± 0.7) and dinner (1.4 ± 0.8 and 1.4 ± 0.8) for less-processed whole grains and finely milled whole grains, respectively.

Measures of glycemia are shown in Table 3. The mean iAUC of the 3 h following all the breakfast meals was 9% (95% CI 3–15) lower during the

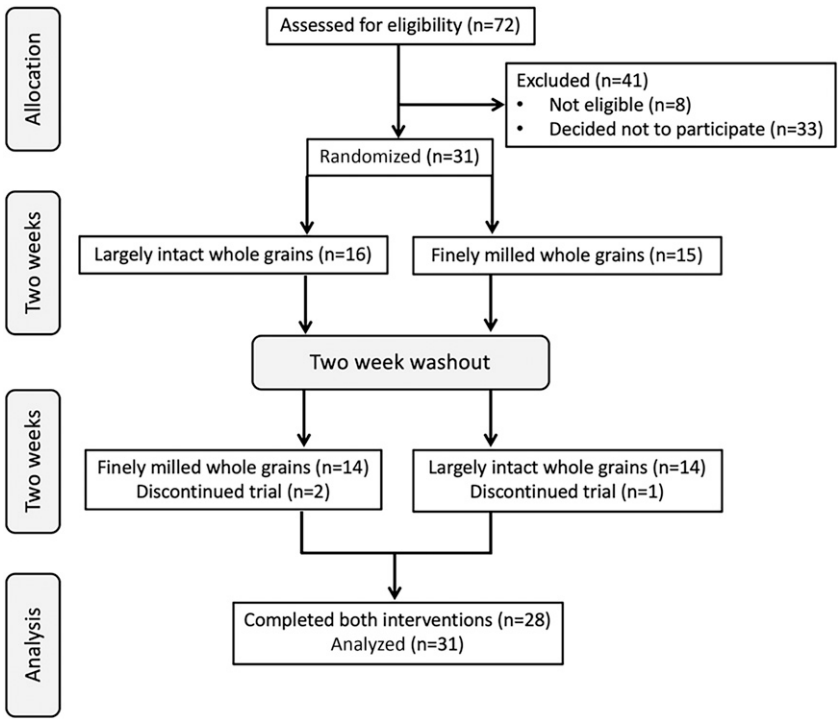

Figure 1—Flowchart of participants through the study.

Table 1—Nutrient information of intervention foods

	Less-processed whole-grain intervention			Finely milled whole-grain intervention		
	Traditional oats (cooked)	Brown rice (cooked)	Coarsely milled bread	Instant oats (cooked)	Brown rice pasta (cooked)	Finely milled bread
Nutrients per 100 g						
Energy (kJ)	512	850	862	512	822	852
Carbohydrates (g)	18.4	39.5	35.77	18.4	40.5	36.49
Protein (g)	4.8	4.9	6.99	4.8	4.3	7.03
Fat (g)	2.3	2.2	2.45	2.3	1.6	1.79
Fiber (g)	4.0	1.6	9.2	4.0	1.4	9.1
Sodium (mg)	<5	<5	290	<5	6.5	290
Retention of whole grains on particle-size sieves (μm), %						
>2,800	93	0	23	40	0*	0
1,000–2,799	7	100	39	52	0*	0
180–999	0	0	16	4	6*	59
<180	0	0	22	4	94*	41

*These measurements were made on brown rice flour as the only listed ingredient in brown rice pasta.

2 weeks of consuming less-processed whole grains than during the weeks when finely milled whole grains were consumed. The mean postprandial response to the average of all meals showed a similar trend, being 6% (1–10) lower. Glycemic variability reduced when participants consumed the less-processed whole grains compared with the finely milled whole grains as measured by MAGE (−0.36 [95% CI −0.65 to −0.08]) and the SD of the mean glucose value (−0.16 mmol/L [95% CI −0.25 to −0.06]). The study was not powered to consider differences in response between participants on the basis of sex or ethnicity.

Anthropometric measures and cardiometabolic risk factors measured preintervention and after each intervention are shown in Table 4. Body weight increased during the finely milled whole-grain intervention and decreased when less-processed whole grains were consumed, resulting in a statistically significant mean difference in weight change (0.81 kg [95% CI 0.62–1.05]). This change in body weight was not a mediating factor for the glycemic variables considered (Table 3**)**. There were no differences observed between interventions for blood lipids, insulin, inflammatory markers, or blood pressure.

CONCLUSIONS

Consuming less-processed whole-grain foods over 2 weeks improved measures of glycemia in free-living adults with type 2 diabetes compared with an equivalent amount of whole-grain foods that were finely milled to reduce their particle size. All whole-grain foods met the definition of being 100% whole grain and had a similar composition in terms of dietary fiber and macronutrients. Whole-grain foods derived from wheat, oats, and brown rice were provided ad libitum to participants, with the amount consumed balanced between interventions. The reduction in glycemia was particularly striking after breakfast, when more servings of whole-grain foods were eaten than at other times during the day. Measures of day-long glycemic variability also improved, suggesting potential benefits in terms of reduced protein glycation and cardiovascular risk (20–22). Although the

Table 2—Nutrient intakes pretrial and during both interventions

Nutrient	Prestudy	Less-processed whole grains	Finely milled whole grains	*P* value difference between interventions
Energy (kJ)	8,820 ± 1,936	9,027 ± 2,669	9,141 ± 2,171	0.858
Fat (%TE)	35 ± 6	30 ± 5	31 ± 6	0.455
Carbohydrates (%TE)	46 ± 7	52 ± 6	51 ± 7	0.641
Protein (%TE)	19 ± 4	17 ± 4	17 ± 3	0.914
Saturated fat (%TE)	14.0 ± 3.5	12.2 ± 3	12.4 ± 3	0.790
Carbohydrates (g/day)	241.7 ± 55	285.6 ± 84	287.4 ± 65	0.921
Sugar (g/day)	83.1 ± 30	78.0 ± 34	80.6 ± 29	0.603
Starch (g/day)	133.9 ± 38	166.0 ± 54	167.3 ± 46	0.937
Fiber (g/day)	25.8 ± 9	40.0 ± 11	38.3 ± 11	0.300
Carbohydrates at breakfast (g/day)	55.8 ± 36.6	61.6 ± 31.9	60.9 ± 31.0	0.616
Carbohydrates at lunch (g/day)	49.9 ± 30.3	55.0 ± 32.1	55.8 ± 33.1	0.841
Carbohydrates at dinner (g/day)	67.4 ± 35.5	75.3 ± 45.4	77.9 ± 42.7	0.951

Data are mean ± SD. Variables that differed in both interventions from prestudy intakes were fat and carbohydrate (%TE) as well as carbohydrates, starch, and fiber (g/day). %TE, percentage of total energy provided to the diet by that macronutrient.

Table 3—Measures of glycemia calculated from CGM

Measure	Less-processed whole grains	Finely milled whole grains	*P* value difference between interventions	*P* value interaction with weight change
Meal responses (mmol/L/min)				
All-meal iAUC	423 ± 210	466 ± 192	0.022	0.555
Breakfast iAUC	449 ± 256	525 ± 248	0.007	0.984
Lunch iAUC	412 ± 287	440 ± 304	0.614	0.321
Dinner iAUC	391 ± 293	415 ± 277	0.117	0.118
24-h measures				
Hours spent in range (3.9–10 mmol/L)	15.49 ± 6.77	15.18 ± 6.74	0.466	0.383
Hours spent above range (>10 mmol/L)	7.90 ± 7.02	8.22 ± 7.12	0.736	0.305
Hours spent below range (<3.9 mmol/L)	0.61 ± 1.65	0.82 ± 2.30	0.602	0.812
Measures of glycemic variability				
MAGE	5.61 ± 2.75	5.94 ± 2.60	0.014	0.193
CONGA	8.07 ± 2.49	8.20 ± 2.85	0.496	0.699
SD of daily mean (mmol/L)	2.33 ± 1.07	2.51 ± 1.10	0.002	0.803

Data are mean ± SD. All values have been log-transformed to address skew. CONGA, continuous overall improvement in net glycemic action.

only difference between the two intervention periods related to whole-grain structure as determined by milling and the reported energy intake did not differ, a different pattern of weight change was observed. Consumption of the less-processed whole-grain foods was associated with a mean reduction of body weight, whereas there appeared to be a modest increase during the 2-week period where finely milled whole-grain foods were provided. There was no indication that the weight difference explained the improvements in glycemia associated with the less-processed whole-grain foods characterized by larger particle size.

Several plausible mechanisms could explain the overall observation that the degree of whole-grain processing, as characterized by whole-grain particle size as a result of milling, alters starch digestibility. First, less-processed whole grains may pass through the small intestine to be digested in the colon by the microbiome into short-chain fatty acids (23), which are absorbed without altering circulating blood glucose levels. Second, smaller whole-grain particle size associated with milling allows water and enzymes easier access to the starch and enables catalytic activity, which alters the rate of glucose absorption (24). Third, the milling of whole grains to flour removes the compartmentalization of starch, affecting starch and protein interactions, which may further affect digestion rate (25). The differing pattern in body weight change between the interventions was unexpected. However, there are several possible explanations. A higher proportion of the intact whole grain may have escaped digestion in the small intestine to be either metabolized in the large bowel or have avoided anaerobic metabolism entirely. It is also conceivable that digestion of less-processed whole grains may be associated with a greater thermic effect than the digestion of whole grains that are more finely ground (26).

A body of work supports benefits in postprandial glycemia when comparing whole-grain consumption with refined grains (27). Fewer studies have considered glycemia following the consumption of intact or processed whole grains (11,28–30). To our knowledge, the longest intervention relevant to this issue by Järvi et al. (28) reported on two different diets followed for 24 days by adults with type 2 diabetes. Diets were nutrient matched and provided the same foods; however, in one diet,

Table 4—Anthropometric, blood pressure, blood lipid, and inflammation measures

	Intervention				
	Less-processed whole grains		Finely milled whole grains		
Measure	Pre	Post	Pre	Post	*P* difference between interventions
Weight (kg)	92.9 ± 21.1	92.4 ± 20.8	93.6 ± 21.0	94.0 ± 21.3	0.002
BMI (kg/m^2)	32.5 ± 7.0	32.2 ± 6.8	32.8 ± 6.9	32.9 ± 7.0	0.001
Fat mass (%)	36.1 ± 10.9	35.6 ± 11.2	37.2 ± 10.7	37.1 ± 11.0	0.312
Systolic BP (mmHg)	130 ± 15	134 ± 17	134 ± 17	134 ± 15	0.161
Insulin* (pg/mL)	497 ± 553	425 ± 373	414 ± 324	452 ± 513	0.234
Total cholesterol (mmol/L)	4.17 ± 1.11	3.94 ± 1.16	4.38 ± 1.35	4.10 ± 1.22	0.346
LDL cholesterol (mmol/L)	2.11 ± 0.90	1.96 ± 0.89	2.22 ± 0.84	2.06 ± 0.86	0.803
HDL cholesterol* (mmol/L)	1.32 ± 0.42	1.26 ± 0.40	1.30 ± 0.38	1.27 ± 0.38	0.312
Triglycerides* (mmol/L)	1.64 ± 0.85	1.61 ± 0.82	1.58 ± 0.87	1.55 ± 0.99	0.954
CRP* (mg/L)	3.73 ± 3.95	3.66 ± 4.31	3.75 ± 3.53	3.27 ± 3.11	0.052
AGP* (g/L)	0.74 ± 0.24	0.82 ± 0.28	0.66 ± 0.26	0.64 ± 0.25	0.131

Data are mean ± SD. AGP, α-1-acid glycoprotein; BP, blood pressure; CRP, C-reactive protein. *Log-transformed to address skew.

the carbohydrate-dense foods, including whole grains, were milled, reducing particle size to produce a difference in glycemic index. Following the interventions, glucose was assessed over 1 day in a controlled setting. As with the current study, Järvi et al. reported improved glycemia following the intervention with less-processed foods of larger particle size. Older acute studies considering the structural integrity of whole grains on postprandial glycemia also confirm our findings (29,31,32). More recently, we have shown an inverse trend between postprandial glycemia and whole-grain particle size in breads in a controlled setting (11).

Current definitions of whole grains permit a wide range of processing methods and require that reconstitution of grain components is to the same ratio as they exist in an intact grain (7,8). The findings of this trial have immediate relevance to clinical guidelines for diabetes management, which currently recommend diets high in whole-grain foods without reference to grain structure or particle size (5,6,33). Given that other health benefits of whole-grain foods (1,9) may also be influenced by their processing, our data provide evidence for a review of the definition of the term whole grain by relevant authorities. A revised definition may reduce the number of health or content claims made for a range of ultraprocessed foods by virtue of their whole-grain content. Such products can also have high contents of sodium, free sugars, or saturated fats as well as total calories.

This trial has a number of strengths. Participants were free living and consuming the provided whole-grain foods within the context of their usual diet, increasing the generalizability of these results. As far as we are aware, this is the first study of this topic to use CGM systems. This has enabled more intensive blood glucose monitoring than has previously been possible and consideration of day-long glycemic variability and daily time spent in range and while hyperglycemic and hypoglycemic. Furthermore, this study used alkylresorcinols in plasma, providing an objective measure of adherence to the whole-grain interventions. The absence of objective measures of intervention adherence is a recognized limitation of previous studies. The trial does have some limitations. It was of insufficient duration to observe potential changes in HbA_{1c} or the lipid profile. The trial was insufficiently powered to consider subgroup analyses according to participant glycemic control, medication type, sex, or ethnicity. The trial was also insufficiently powered to consider specific whole-grain foods or other variables that may influence the outcomes measured. Finally, the participants of this trial were volunteers who are not necessarily representative of the population of people with type 2 diabetes and, therefore, may be more likely to adhere to the trial interventions (34). Future larger and longer studies are planned to resolve these questions.

Consuming less-processed whole-grain foods achieved an improvement in postprandial glycemia and other indices of glycemic control in adults with type 2 diabetes compared with consuming whole-grain foods where the grain particle size was further reduced through milling. These findings suggest that maintaining the structural integrity of whole grains in foods available for consumption will likely have long-term health benefits. Our findings are highly relevant to nutritional guidelines for diabetes management and suggest practical means for those wishing to improve their blood glucose control. They may also contribute to discussion regarding a revision of the definition of the term whole grains and, consequently, use of the term in front-of-pack labeling claims.

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