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Editorial Board

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Editorial

Whole Grains, Legumes, and Health

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The consumption of whole grains and legumes is recommended by public health agencies around the world. The recommendation to consume legumes is based on them being a good source of protein, fiber, and several micronutrients including iron and zinc. However, legumes tend to be consumed infrequently by many people in industrialized countries. Dietary interventions with legumes have yielded mixed results on health outcomes, and there may be reluctance by some people to increase the amount of legumes in their diets due to unfamiliarity with the food.

The recommendations for whole grains are based on purported health benefits of consuming whole grain over refined grain products. In comparison with their refined counterparts, whole grain foods tend to be higher in phytochemicals and fiber, and in several micronutrients including some of the B vitamins, magnesium, and selenium. Based on subjective dietary intake data, observational studies are reasonably consistent in their findings that higher cereal fiber and magnesium intakes are associated with lower risk of type 2 diabetes and cardiovascular disease. An objective marker of whole-grain intake would be useful, and in this regard, alkylresorcinols, compounds present in the bran particularly of wheat and rye, can be measured in biological fluids as potential biomarkers of wheat and rye intake.

Despite the recommendations, interventions with whole-grain foods have produced mixed results on health markers. One factor contributing to the variability in outcomes may be grain structure. Intact grain structure distinguishes "whole grain" from "whole meal," a process in which the whole grains have been ground. The starch contained in an entirely or partially intact grain is surrounded by the fibrous seed coat. Chewing helps to release the starch from within the seed coat; however, not all of the starch will be released, and access by digestive enzymes will be hindered. This hindrance is often regarded as a good quality as it slows starch digestion and glucose absorption, aiding blood glucose control. Another factor in starch digestion is the type of fiber. Some grain fibers are water soluble and highly fermentable, and form viscous gels. The formation of the gels also slows down starch digestion and glucose absorption. A third factor associated with improved blood glucose control is the "subsequent meal effect," a phenomenon in which the benefit of slowly absorbed carbohydrate on blood glucose at one meal is extended to the meal following. Thus, the recommendations to consume whole grain foods are supported by mechanistic plausibility, whilst the variability in outcomes of whole-grain and legume intervention studies may be related to differences in study design and compliance.

This special issue of the Journal of Nutrition and Metabolism explores some of the issues regarding the consumption of whole grains and legumes on health outcomes. It comprises three review and two research articles. Included is a comprehensive review of studies describing the "subsequent meal effect" in which mechanisms for the effect are discussed and research challenges suggested. The status of alkylresorcinols as biomarkers of whole-grain intake is presented that includes suggestions for further validation work and recommendations on how this might be achieved. The health benefits of beta-glucan, a fiber found in oat and barley bran, are reviewed including discussion of its effect when consumed as a component of the whole grain or as an extracted product. Mechanisms of action and challenges in the use of beta-glucans are discussed. The effect on postprandial blood glucose of incorporating whole

grains into bread is reported with comparisons made among sprouted-grain, sourdough, and mixed grain breads in a group of overweight and obese men. At the other end of the nutritional spectrum, the effects of using locally grown grains and legumes as a porridge base with which to feed undernourished children are presented.

General recommendations to consume whole-grain and legume foods appear to be well founded although there is much work to be done to identify grain/legume types, components, and intakes consistent with well-being among people of varying demographics and states of health. We hope that topics raised in this special issue lead to further research aimed at advancing our knowledge pertaining to whole-grain and legume consumption leading to strong evidence-based intake recommendations.

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Research Article

The Acute Impact of Ingestion of Sourdough and Whole-Grain Breads on Blood Glucose, Insulin, and Incretins in Overweight and Obese Men

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Consumption of whole-grain and sourdough breads is associated with improved glucose homeostasis. We examined the impact of commercial breads on biomarkers of glucose homeostasis in subjects at risk for glucose intolerance. In a randomized, crossover study, overweight or obese males ingested 11-grain, sprouted-grain, 12-grain, sourdough, or white bread on different occasions, matched for available carbohydrate (50 g) in part 1 ($n = 12$) and bread mass (107 g) in part 2 ($n = 11$), and blood glucose, insulin and glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) were determined for 3 h. In part 1, glucose response for sprouted-grain was lower than 11-grain, sourdough, and white breads. Insulin area under the curve (AUC) for sourdough and white was lower than 11-grain and sprouted-grain breads. GLP-1 response to sourdough was lower than all breads. In part 2, glucose and insulin AUC for sourdough was greater than 11-grain, sprouted-grain, and 12-grain breads. Sprouted-grain bread improved glycemia by lowering glucose response and increasing GLP-1 response. In overweight and obese men, the glycemic response to sprouted grain bread was reduced in both parts 1 and 2 while the other whole-grain test breads did not improve metabolic responses in the acute postprandial state.

1. Introduction

There is substantial interest in the role of dietary carbohydrate (CHO) in preventing and managing type 2 diabetes (T2D) [1]. In North America, bread is the predominant CHO-containing food, and consumption of white bread is 5 times that of whole wheat, rye, and other dark breads [2]. Replacing white bread with whole-grain breads is often recommended to improve glycemic control [3]. Epidemiologic studies have reported inverse associations between whole-grain consumption and the risk of T2D and cardiovascular disease [4–8], and clinical studies [9, 10] have reported beneficial effects of whole-grain consumption on the metabolic profile of subjects with impaired glycemic control. It has been suggested that the fiber content of whole-grain foods improves glucose/insulin metabolism by reducing the rate of CHO breakdown and absorption [11–13].

The incretin hormones, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide-1 (GLP-1) are intimately involved in postprandial regulation of glucose homeostasis. It is estimated that approximately half of the postprandial insulin release in response to CHO ingestion is caused by these gut-derived hormones [14–17]. Thus, the magnitude of the incretin response is vital to both the acute insulinemic and glycemic responses to CHO ingestion. However, our understanding of the impact of different types of CHO on the incretin response is still in its infancy.

Previously, we showed that ingestion of whole-wheat and whole-wheat barley breads did not result in attenuated insulin responses compared with white bread [18]. Furthermore, sourdough white bread resulted in lower glucose and GLP-1 responses for two subsequent meal periods [18]. In our previous work, ultrafinely grounded whole-wheat flour was used rather than whole-grain flour. In addition, in

order to equalize the amount of available CHO (50 g) across treatments, the bread mass consumed varied from 98 to 138 g resulting in higher energy, fat, protein, and fiber intake for the whole-wheat bread treatments [18]. Further study is needed to examine if bread mass influences the metabolic responses to bread.

The sprouting treatment of cereal grains is reported to decrease starch content and increase the content and availability of vitamins, minerals, and antioxidants [19]. One clinical study reported improved glycemia following consumption of pregerminated brown rice, compared to white rice, in healthy and type T2D subjects [20]. The metabolic effect of breads baked with sprouted wheat flour has not been extensively studied.

The present investigation had a distinct applied nature and tested the hypothesis that consumption of laboratory-prepared sourdough bread and commercially available whole-grain and sprouted-grain breads would result in lower metabolic responses compared with commercial, white bread in subjects who are at risk for glucose intolerance and T2D. This hypothesis was tested using 2 approaches including normalizing consumption of breads according to available CHO (part 1) and bread mass (part 2).

2. Materials and Methods

The study protocol was approved by the University of Guelph Human Research Ethics Board and each subject provided written informed consent. Subjects were recruited from the Guelph, Ontario area through advertisement in local newspapers. Subjects were overweight or obese males (body mass index (BMI): 25–35 kg/m^2), nonsmokers and had no history of gastrointestinal disease, gluten allergy, dyslipidemia, or diabetes. Subjects did not take medications (with the exception of antidepressants and/or antihypertensives) or natural health products. Potential subjects were screened for glucose intolerance and diabetes at a prestudy visit using a standard 2 h oral glucose tolerance test (OGTT) (Trutol Custom Laboratories Inc., Baltimore, MD). Subjects were excluded if they had impaired fasting plasma glucose (>6.1 mmol/L), impaired glucose tolerance (>7.8 mmol/L at 2 h), or impaired fasting insulin (>90 pmol/L).

2.1. General Protocol. Parts 1 and 2 of the investigation followed the same protocol, with the exception of the quantity of bread consumed. A single-blind, randomized crossover design was used with washout periods of at least 1 week between study days. Throughout the study, subjects were instructed to maintain their usual diet and lifestyle but were instructed to avoid alcohol, caffeine substances and strenuous physical activity 48 h prior to each study day and to report to the laboratory after an overnight (12 h) fast. Dietary records were kept for three days prior to each study day and in the evening before each study day, subjects were instructed to consume a standardized meal, consisting of vegetable lasagne (President's Choice Blue Menu Reduced Fat Vegetable Lasagne) and a cereal bar (Kellogg's Nutri-Grain Cereal Bar).

Table 1: Nutrient composition of the test breads delivering 50 g available CHO (part 1)[1].

	11-grain	Sprouted-grain	Sourdough	12-grain	White
Total bread (g)	151.0	157.2	107.3	122.2	110.3
Available CHO (g)[2]	50.0	50.0	50.0	50.0	50.0
Energy (kcal)	320.2	336.4	277.9	317.8	273.7
Starch (g)	44.9	46.3	45.4	42.5	43.6
Total sugars (g)	5.1	3.6	4.5	7.4	6.4
Soluble fiber (g)	0.9	0.6	0.3	1.1	0.3
Insoluble fiber (g)	11.9	11.4	4.9	9.9	4.6
Dietary fiber (g)	12.8	12.1	5.2	11.0	4.9
Protein (g)	16.9	22.3	9.0	12.6	9.8
Fat (g)	3.1	2.9	4.3	5.2	3.6

[1] Test breads were analyzed by Laboratories of Canada Incorporated (ILC) in Tillsonburg, ON.
[2] Available CHO was calculated using this formula: starch + total sugar.

On each study day, a venous catheter was inserted into the forearm by a trained technician and kept patent for the duration of the experiment with a slow saline infusion. After collection of a fasting blood sample (time point −15 min), subjects consumed a serving of test bread with 250 mL of water within 15 min. The laboratory clock started when subjects commenced eating the bread, and after 15 min (time point zero) the second blood sample was collected. Subsequently, blood samples were collected at 15, 30, 45, 60, 90, 120, 150, and 180 min.

2.1.1. Part 1: Acute Postprandial Effect of Ingestion of Breads Matched for Available Carbohydrate. Twelve overweight or obese males were recruited in part 1. The test breads were prepared to provide 50 g of available CHO which required portions of 151 g for 11-grain (whole-grain, with sourdough culture, Stone-mill Bakehouse Ltd., Scarborough, ON, Canada), 157 g of sprouted-grain (whole-grain, with sourdough culture, Stone-mill Bakehouse Ltd., Scarborough, ON, Canada), 107 g of sourdough white (as described previously [18] and baked at the Guelph Food Technology Centre at the University of Guelph), 122 g of 12-grain (whole-grain, Dempsters, Canada Bread Ltd., Brampton, ON, Canada), and 110 g of white bread (Wonder Bread, Weston Bakeries Ltd., Toronto, ON, Canada) (Table 1). Breads were sliced, decrusted and stored at −20°C until consumption. Before consumption, the bread slices were thawed in a microwave oven for 15 s and weighed.

2.1.2. Part 2: Acute Postprandial Effect of Ingestion of Breads Matched for Mass. Eleven overweight or obese males completed part 2, 9 of whom also completed part 1. The same test

Table 2: Nutrient composition of the test breads delivering a consistent portion size (part 2)[1].

	11-grain	Sprouted-grain	Sourdough	12-grain	White
Total bread (g)	107.3	107.3	107.3	107.3	107.3
Available CHO (g)[2]	35.5	34.0	50.0	43.8	48.6
Energy (kcal)	227.4	229.6	277.9	278.9	266.0
Starch (g)	31.2	31.6	45.4	37.3	42.3
Total sugars (g)	4.3	2.4	4.5	6.5	6.2
Soluble fiber (g)	0.6	0.4	0.3	0.9	0.3
Insoluble fiber (g)	8.4	7.8	4.9	8.6	4.5
Dietary fiber (g)	9.1	8.2	5.2	9.6	4.8
Protein (g)	12.0	15.2	9.0	11.0	9.5
Fat (g)	2.2	2.0	4.2	4.6	3.5

[1] Test breads were analyzed by Laboratories of Canada Incorporated (ILC) in Tillsonburg, ON.
[2] Available CHO was calculated using this formula: starch + total sugar.

breads studied in part 1 were prepared to provide a consistent portion of 107 g. This volume was selected as it allowed for a comparison between parts 1 and 2 for the ingestion of the same quantity of the sourdough bread. This resulted in portions of 35, 34, 50, 43, and 48 g of available CHO for 11-grain, sprouted-grain, sourdough white, 12-grain, and white bread, respectively (Table 2).

2.2. Blood Collection, Biochemical and Dietary Analysis. For analysis of blood glucose, blood samples were collected at all time points into vacutainers containing 72 USP units sodium heparin, immediately put on ice, and subsequently analyzed using a semiautomatic glucose analyzer (YSI 2300, Yellow Springs, OH, USA). For analysis of serum insulin, blood samples were collected at all time points into vacutainers without anticoagulants and centrifuged (1341 ×g for 10 min at 4°C). Serum supernatant was aliquoted and frozen at −20°C until analysis using a solid phase ^{125}I radioimmunoassay (Coat-A-Count, Diagnostic Products Corporation, CA, USA) with an intra- and interassay variability of 5.2% and 7.3%, respectively.

For analysis of the incretin hormones, blood samples were collected at all time points into ice-chilled tubes containing 10.8 mg K_2EDTA, 1824 KIU aprotinin, and 10 μL/mL blood dipeptidyl peptidase-4 inhibitor. Following centrifugation (1000 ×g for 15 min at 4°C), plasma was separated and stored at −80°C until analysis. Plasma GIP total concentrations were measured using a Human GIP (Total) ELISA kit (Linco Research Inc., St Charles, USA) with 100% crossreactivity to human intact GIP, GIP (1–42), and the N-terminally truncated metabolite, GIP (3–42). Intra- and interassay variability for GIP were 6.5% and 3.4%, respectively. Plasma GLP-1 total concentrations were measured by GLP-1 total RIA kit (Linco Research Inc., St Charles, USA) after extraction with 70% ethanol. The antibody used in this kit binds specifically with C-terminal portion of GLP-1, both amidated and nonamidated forms. Intra- and interassay variations for GLP-1 were 4.0% and 9.9%, respectively.

Food record data were analyzed for energy, macronutrients, cholesterol, and dietary fiber by using ESHA Food Processor program (version 9.5, Salem, OR, USA) and averaged across each 3-day food record.

2.3. Calculations and Statistical Analysis. Incremental area under the curve (AUC) was determined for blood glucose, serum insulin, plasma GIP, and GLP-1 (GraphPad Prism, version 3.02, San Diego, CA, USA). Prism computes the incremental area under the curve by using the trapezoid rule. Time point −15 was used as the baseline, and values below the baseline were considered to be negative peaks. Insulin Sensitivity Index (ISI) was calculated using the method described by Matsuda and DeFronzo [21].

All statistical analyses were performed using the Statistical Analysis System (SAS Institute Inc., version 9.1 Cary, NC, USA). Univariate analysis was used to examine the distribution of each variable, and logarithmic transformations were applied to data that was not normally distributed (specific variables are identified in data tables). Significance ($P < 0.05$) was tested by two-factor repeated measure analysis of variance (ANOVA) using a mixed model (treatment: fixed effect and subject: random effect) followed by the Tukey's test for multiple comparisons. Results are presented as mean ± SEM.

3. Results

3.1. Part 1: Acute Postprandial Effect of Ingestion Breads Matched for Available CHO

3.1.1. Subjects. Twelve subjects (age: 54.9 ± 2.0 y, BMI: 29.1 ± 1.1 kg/m^2, fasting blood glucose: 4.5 ± 0.1 mmol/L, fasting serum insulin: 50.8 ± 4.8 pmol/L) completed part 1 of the study.

3.1.2. Blood Glucose. Significant overall treatment effects were found in glucose responses to the breads (Figure 1). Sprouted-grain bread was significantly lower than 11-grain ($P < 0.009$), sourdough ($P < 0.001$), and white ($P < 0.006$) breads. Furthermore, 12-grain bread was significantly lower than 11-grain ($P < 0.04$) and sourdough ($P < 0.003$) breads. Similarly, glucose incremental AUC for sprouted-grain bread was significantly lower than 11-grain ($P < 0.007$), sourdough ($P < 0.004$), and white ($P < 0.05$) breads (Table 3). Furthermore, glucose incremental AUC for 12-grain bread was significantly lower than 11-grain ($P < 0.01$) and sourdough ($P < 0.009$) breads (Table 3).

3.1.3. Serum Insulin and Insulin Sensitivity. Significant overall treatment effects were found in insulin responses to the

Table 3: Incremental area under the curve for blood glucose, serum insulin, plasma GIP and GLP-1 after ingestion of 50 g available CHO of the test breads for 180 min (part 1)[1,2].

	11-grain	Sprouted-grain	Sourdough	12-grain	White
Glucose (mM/L·min)	$0.64^{a} \pm 0.04$	$0.22^{b} \pm 0.17$	$0.66^{a} \pm 0.16$	$0.26^{bc} \pm 11.0$	$0.51^{ac} \pm 0.17$
Insulin (nM/L ∗ 180 min)	$31.6^{a} \pm 6$	$30.4^{a} \pm 5$	$21.4^{b} \pm 3.3$	$25.9^{ab} \pm 6.8$	$24.1^{b} \pm 4.5$
GIP (nM/L ∗ 180 min)	3.2 ± 0.4	3.7 ± 0.3	3.6 ± 0.4	3.6 ± 0.4	3.3 ± 0.2
GLP-1[3] (nM/L ∗ 180 min)	0.58 ± 0.23	0.57 ± 0.32	-0.04 ± 0.16	0.38 ± 0.2	0.41 ± 0.31

[1] All values are mean (±SEM); ($n = 12$) except for GLP-1 ($n = 11$) because of technical problems.
[2] Mean values within a row with different superscript letters were significantly different ($P < 0.05$).
[3] Data was log-transformed prior to statistical analysis and is presented as the geometric mean ± SEM.

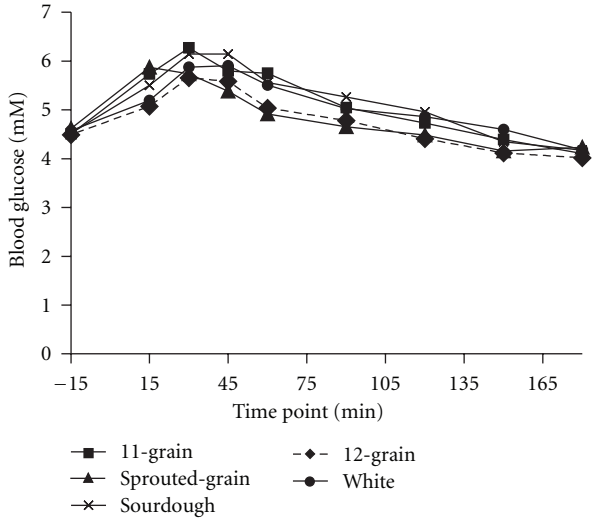

Figure 1: Fasting and postprandial glucose responses to the ingestion of 50 g available carbohydrate of the test breads. Data are means. Standard errors are not included for clarity, $n = 12$. Test bread was ingested after collection of fasting blood sample at time point −15 min. Significant overall treatment effects were found in glucose responses to the breads (Sprouted-grain bread was lower than 11-grain ($P < 0.009$), sourdough ($P < 0.001$), and white ($P < 0.006$) breads). Twelve-grain bread was lower than 11-grain ($P < 0.04$) and sourdough ($P < 0.003$) breads).

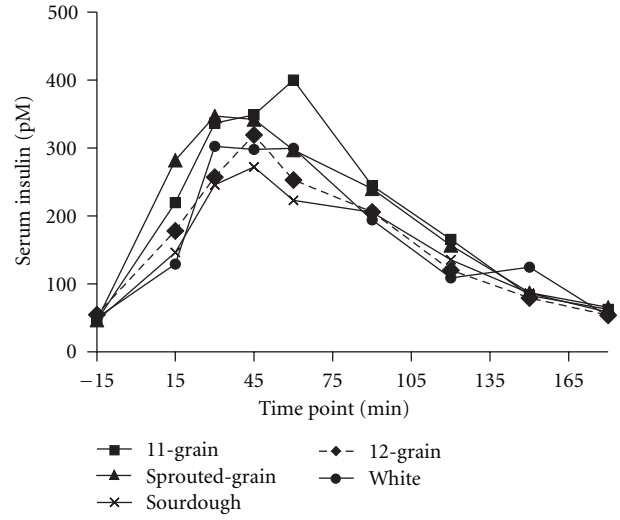

Figure 2: Fasting and postprandial insulin response to the ingestion of 50 g available carbohydrate of the test breads. Data are means. Standard errors are not included for clarity, $n = 12$. Test bread was ingested after collection of fasting blood sample at time point −15 min. Significant overall treatment effects were identified (11-grain bread was greater than sourdough ($P < 0.005$) and white ($P < 0.03$) breads).

breads with 11-grain bread being higher than sourdough ($P < 0.005$) and white ($P < 0.03$) breads (Figure 2). Furthermore, insulin incremental AUC for 11-grain and sprouted-grain breads was significantly ($P < 0.05$) greater than sourdough and white breads (Table 3). ISI was not significantly different among the breads (data not shown).

3.1.4. Plasma GIP and GLP-1. Despite the difference in insulin responses, there was no significant overall treatment effect in GIP responses to the breads (data not shown). Similarly, bread treatment did not significantly affect GIP incremental AUC (Table 3). The significant differences in overall GLP-1 response to the breads did not correspond with those for insulin. The GLP-1 response to sourdough bread was lower than 11-grain ($P < 0.0001$), sprouted-grain ($P < 0.0001$), and white ($P < 0.02$) breads. Additionally, the GLP-1 response to 11-grain bread was greater than 12-grain ($P < 0.03$) and white ($P < 0.03$) breads, while the GLP-1 response to sprouted-grain bread was greater than 12-grain ($P < 0.009$) and white ($P < 0.05$) breads (Figure 3). Despite these differences, bread treatment did not significantly affect GLP-1 incremental AUC (Table 3).

3.2. Part 2: Acute Postprandial Effect of Ingestion of Breads Matched for Mass

3.2.1. Subjects. Eleven subjects (age: 53.9 ± 1.7 y, BMI: 28.6 ± 0.7 kg/m^2, fasting glucose: 4.6 ± 0.1 mmol/L, fasting insulin: 40.6 ± 5.7 pmol/L) completed part 2 of the study.

3.2.2. Blood Glucose. Although there were no significant overall treatment effects in glucose responses to the breads, glucose incremental AUC for sourdough bread was significantly greater than 11-grain ($P < 0.002$), sprouted-grain ($P < 0.01$), 12-grain ($P < 0.001$), and white ($P < 0.04$) breads (Table 4).

Table 4: Incremental area under the curve for blood glucose, serum insulin, plasma GIP and GLP-1 responses to the ingestion of set amount of the test breads for 180 min (part 2)[1,2].

	11-grain	Sprouted-grain	Sourdough	12-grain	White
Glucose (mM/L·min)	$0.31^{a} \pm 0.12$	$0.17^{a} \pm 0.15$	$0.72^{b} \pm 0.19$	$0.41^{a} \pm 0.11$	$0.46^{a} \pm 0.14$
Insulin (nM/L ∗ 180 min)	$16.2^{ac} \pm 2.1$	$12.7^{ac} \pm 1.9$	$21.5^{b} \pm 2.7$	$16.8^{a} \pm 2.4$	$18.1^{bc} \pm 3.4$
GIP (nM/L ∗ 180 min)	$2.7^{a} \pm 0.3$	$3.1^{ab} \pm 0.3$	$3.5^{bc} \pm 0.3$	$3.3^{ac} \pm 0.4$	$4.0^{b} \pm 0.7$
GLP-1[3](pM/L ∗ 180 min)	$0.48^{ab} \pm 0.2$	$0.83^{a} \pm 0.3$	$-0.05^{b} \pm 0.1$	$-0.19^{b} \pm 0.5$	$0.07^{ab} \pm 0.3$

[1] All values are mean (±SEM); ($n = 11$) except for GLP-1 ($n = 10$) because of technical problems.
[2] Mean values within a row with different superscript letters were significantly different ($P < 0.05$).
[3] Data was log transformed prior to statistical analysis and is presented as the geometric mean ± SEM.

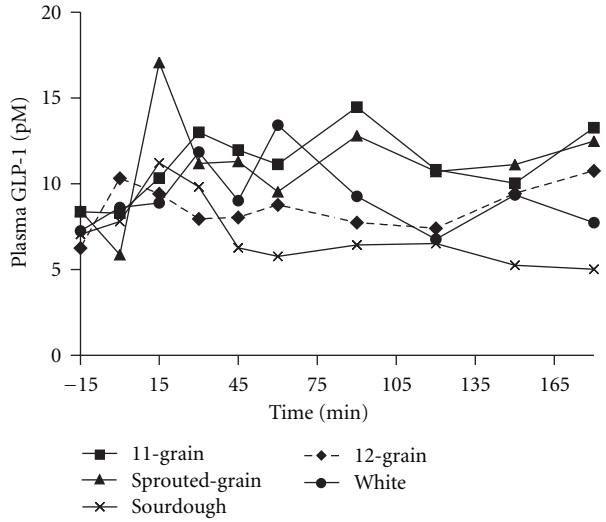

Figure 3: Fasting and postprandial GLP-1 responses to the ingestion of 50 g available carbohydrate of the test breads. Data are means. Standard errors are not included for clarity, $n = 11$. Test bread was ingested after collection of fasting blood sample at time point −15 min. Significant overall treatment effects were found (sourdough bread was lower than 11-grain ($P < 0.0001$), sprouted-grain ($P < 0.0001$), and white ($P < 0.02$) breads. 11-grain bread was greater than 12-grain ($P < 0.03$) and white ($P < 0.03$) breads. Sprouted-grain bread was greater than 12-grain ($P < 0.009$) and white ($P < 0.05$) breads).

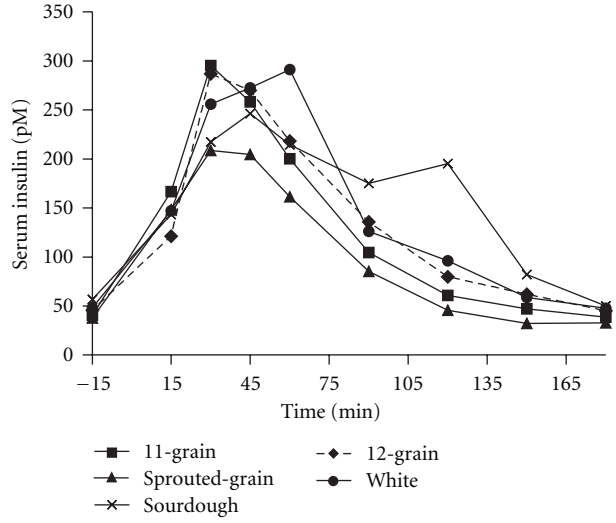

Figure 4: Fasting and postprandial insulin responses to the ingestion of a consistent amount of the test breads. Test bread was ingested after collection of fasting blood sample at time point −15 min. Data are means. Standard errors are not included for clarity, $n = 11$. Significant overall treatment effects were found in insulin response to the breads (sprouted-grain bread was lower than 12-grain ($P < 0.03$) bread, and 12-grain bread was lower than sourdough ($P < 0.001$) and white ($P < 0.001$) breads).

3.2.3. Serum Insulin and Insulin Sensitivity. Significant overall treatment effects were found in insulin responses to the breads with sprouted-grain being lower than 12-grain ($P < 0.03$) bread and 12-grain bread being lower than sourdough ($P < 0.001$) and white ($P < 0.001$) breads (Figure 4). Insulin incremental AUC for 11-grain ($P < 0.03$), sprouted-grain ($P < 0.05$), and 12-grain ($P < 0.0007$) breads was significantly lower than sourdough bread. In addition, insulin incremental AUC for 12-grain was lower than white bread ($P < 0.03$) (Table 4). ISI was not significantly different among the breads (data not shown).

3.2.4. Plasma GIP and GLP-1. As in part 1, incretin responses did not correspond with the postprandial insulin response. Overall GIP response to 11-grain was lower than sourdough bread ($P < 0.008$) (Figure 5). GIP incremental AUC for 11-grain bread was significantly lower than sourdough ($P < 0.03$) and white ($P < 0.001$) breads (Table 4). Despite the modest (4.8 g) difference in the available CHO consumed, GIP incremental AUC for 12-grain was lower than white bread ($P < 0.03$) (Table 4).

Similarly, GLP-1 response did not relate to the amount of available CHO consumed as the overall GLP-1 response to sprouted-grain bread was significantly greater than 11-grain ($P < 0.008$), sourdough ($P < 0.001$), 12-grain ($P < 0.04$), and white ($P < 0.04$) breads (Figure 6). GLP-1 incremental AUC for sprouted-grain was significantly greater than sourdough ($P < 0.05$) and 12-grain ($P < 0.01$) breads (Table 4).

4. Discussion

The purpose of the current study was to determine the acute effects of breads of variable carbohydrate composition on postprandial glucose, insulin, and incretin responses in sedentary, overweight/obese males as this population

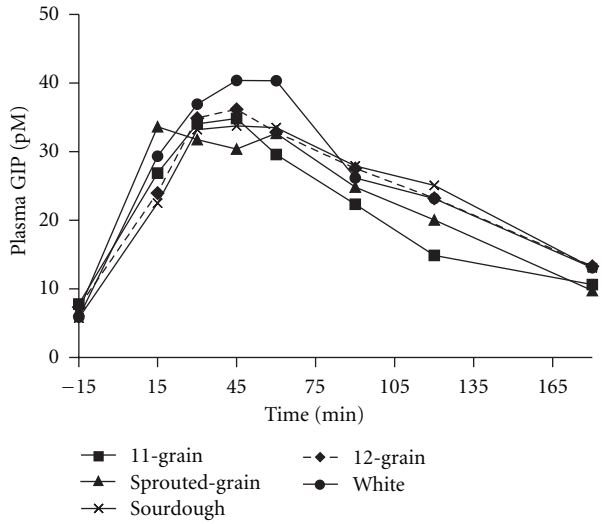

Figure 5: Fasting and postprandial GIP responses to the ingestion of a consistent amount of the test breads. Data are means. Standard errors are not included for clarity, $n = 11$. Test bread was ingested after collection of fasting blood sample at time point −15 min. A significant overall treatment effect was found (11-grain bread was lower than sourdough ($P < 0.008$) bread).

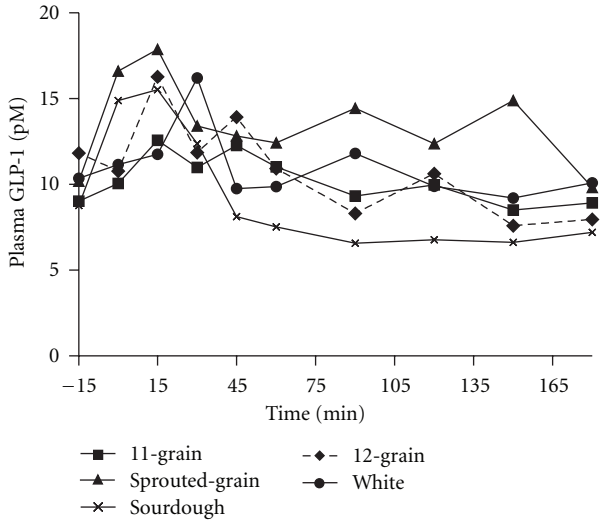

Figure 6: Fasting and postprandial GLP-1 responses to the ingestion of a consistent amount of the test breads. Data are means. Standard errors are not included for clarity, $n = 10$. Test bread was ingested after collection of fasting blood sample at time point −15 min. Significant overall treatment effects were found (sprouted-grain bread was greater than 11-grain ($P < 0.008$), sourdough ($P < 0.001$), 12-grain ($P < 0.04$), and white ($P < 0.04$) breads).

represents a group that are at increased risk for T2D. We hypothesised that the sprouted-grain, whole-grain, and sourdough breads would lower the postprandial metabolic responses, in comparison to white bread, in both parts 1 and 2 of the study. The nature of the subjects and the testing of commercial breads given either in portions based on available CHO or volume are limitations to interpreting the data, but they also are a strength as the findings are very applicable to society. The key findings were that the sprouted grain bread reduced the glycemic responses in both parts of the study and also that generally the whole-grain breads did not have what could be interpreted as beneficial, metabolic responses. While some differences were observed in the incretin hormones, these did not correspond to the insulin responses.

When 50 g of available CHO was ingested (part 1), the glucose response (overall and incremental AUC) to sprouted-grain bread was significantly less than 11-grain, sourdough, and white breads. Additionally, the glucose response (overall and incremental AUC) for 12-grain bread was significantly lower than sourdough and 11-grain breads. The favourable glucose responses to the sprouted-grain and 12-grain breads support our hypothesis. Greater fiber content in sprouted-grain and 12-grain breads (Table 1) may explain the lowered glycemia following their ingestion compared to white and sourdough breads. Dietary fiber is reported to attenuate glycemic response through its physical action in the gut which lowers the rate of CHO digestion and absorption [11, 12, 21–23]. However, the glucose-lowering effect of cereal fiber has been attributed primarily to soluble fiber [12, 22, 24], and in the present study, the fiber content of the sprouted-grain and 12-grain breads was predominantly insoluble fiber, suggesting that soluble fiber may not be the only component responsible for improving glycemia. Other nutrients and components in the sprouted-grain and 12-grain breads may also have positive health-related effects. It has been suggested that the sprouting treatment of cereal grains increases the content and availability of vitamins, minerals, and antioxidants [19], and whole-grains are known to contain higher amounts of vitamins, minerals, antioxidants, and phytochemicals. The presence of micronutrients such as magnesium, vitamin E, antioxidants, phenolic compounds, and phytoestrogens may act synergistically to lower glycemia [6–9, 25, 26].

The lack of significant difference in postprandial glucose response between the 11-grain and white bread was unexpected. It should be noted that there are several factors influencing the metabolic responses to breads including the flour particle size, kneading protocol, leavening process, and baking procedure [27–31], but we are currently unable to identify which specific factor may have accounted for the findings in the present study. A strength of this study is its applicability due to the use of commercially prepared breads, but this also presents a limitation as detailed information regarding ingredients (i.e., the grain/flour structure and proportion contribution to each bread) and processing techniques are not available. Furthermore, although we accept that sample size may be another limitation, our results strongly suggest that there are no acute metabolic differences among the other breads. However, this does not mean there are no benefits in consuming these breads rather that any of the benefits are not obvious within the few hours that we studied. In fact, large epidemiological studies show an inverse relationship with whole grain intake and risk of obesity, diabetes, and cardiovascular disease. A large study

examining almost 43000 people for up to 12 years found that a diet high in whole grains was inversely associated with type 2 diabetes risk [5]. Although the physiological mechanisms remain unclear, the postprandial response to dietary fiber remains a promising mediator of improved health. Conversely, a small randomized crossover study with 30 subjects by Andersson and colleagues [32] aligns with our results suggesting a lack of a favorable postprandial metabolic response to whole grain when compared to refined meals in those who are healthy and slightly overweight. Overall, there is paucity of information on the metabolic responses to breads of varying carbohydrate in overweight and obese men, and investigation with larger sample sizes is warranted to better understand the biological mediators of glycemic control.

While it is possible that any positive effect of the 11-grain bread would be apparent only after a chronic intervention, our findings clearly highlight that whole-grain breads are not the same. Eleven-grain bread was prepared with sourdough culture and contained high amount of fiber and did not improve glycemia; this finding suggests that one cannot generalize across whole-grain products, and the metabolic responses to whole-grains are different for each recipe.

The insulin results did not support our hypothesis. When matched for available CHO, insulin incremental AUCs for 11-grain and sprouted-grain breads were greater than sourdough and white breads (Table 3). This is consistent with the glucose data for sprouted-grain and sourdough breads, but does not explain the glucose result for 11-grain bread, suggesting that glycemia does not always predict insulinemia. In the present study, acute ingestion of 50 g available CHO from whole-grain and sprouted-grain breads did not improve insulinemia or insulin sensitivity (as assessed by calculation of ISI) compared to white bread. Limited literature is available on acute intervention and the results from epidemiologic [4, 5, 7] and chronic interventional [9, 10] studies suggest that any positive effect of whole-grain food intake on insulinemia and insulin sensitivity is only apparent after a chronic intervention. These findings may help explain the lack of positive effect of acute ingestion of whole-grain breads on insulinemia and insulin sensitivity in our study.

It should be noted that the magnitude of the glucose and insulin (Tables 3 and 4) responses to the sourdough bread was similar in parts 1 and 2 of the study, respectively, and that these data are consistent with those reported previously from our laboratory [18]. While we previously showed that sourdough bread resulted in a more favourable postprandial response compared with whole-wheat bread [18], the breads were all prepared in the laboratory. In the present study, the comparison was with whole-grain (not whole-wheat) breads that were commercially prepared. In the former investigation [18], the breads were all administered to control for available CHO and thus subjects ingested different amounts of breads. In part 2 of the current study, matching the treatments for volume of bread consumed resulted in a large difference in available CHO content among the breads. The lower glucose and insulin incremental AUCs for the whole-grain breads compared to those of sourdough bread can be attributed to the lower available CHO and greater dietary fiber content of the whole-grain treatments.

Incretins are potent insulin-releasing hormones that play an important role in glucose homeostasis. Previously we observed that sourdough bread resulted in lower GLP-1 response [18]. In part 1 of the present study, GIP responses to the ingestion of 50 g available CHO of the breads did not differ significantly among the test breads. However, in part 2, ingestion of equal amounts of the test breads resulted in significantly lower GIP incremental AUC for 11-grain and 12-grain breads compared to white breads, a result that may be attributed to the lower available CHO content of these breads. However, the GIP response to sprouted-grain bread, with the lowest available CHO content, was not lower than those to white bread. In both parts 1 and 2, the insulin responses did not appear to follow that of the incretins. These findings suggest that postprandial responses for different whole-grain breads are complex and cannot be explained only by the available CHO content.

Consistent with our previous study [18], in part 1 of the present study, overall GLP-1 response to sourdough bread was significantly lower than 11-grain, sprouted-grain, and white breads. Consistently, insulin response to sourdough bread in part 1 was significantly lower than 11-grain and sprouted-grain breads. Bakhoj et al. [33] reported lowered postprandial GIP responses to the ingestion of Einkorn honey-salt leavened and whole-grain breads compared to the conventional yeast bread and proposed that this was due to an increased level of organic acids (based on reduction of the pH in the dough). Dietary fiber has also been shown to increase GLP-1 secretion in rats [34] and dogs [35]. A study by Massimino et al. [35] found that highly fermentable dietary fibers were more potent stimulators of GLP-1 secretion compared to low fermentable fibers. Given that the fermentable, insoluble fibre content was greatest in the sprouted-grain and lowest in the sourdough bread, it is reasonable to speculate that the GLP-1 response observed in the present study may in part be influenced by insoluble fiber content of the breads. Lastly, it is important to note that a more refined study of incretin dynamics in an animal model may better characterize the transient postprandial nature of these peptides taking into account their relatively short half-lives. In our study, however, we were ethically constrained and only able to draw a certain number of samples that were mixed venous in nature thus why we opted to examine the incretin response as incremental AUC.

Overall, the results of the current investigation suggest that glucose metabolism is complex and multifactorial. The simple model of glucose stimulated insulin secretion, and incretins regulating postprandial insulin release does not always apply. Additionally, GIP and GLP-1 do not respond in a similar manner with respect to the CHO ingested. In our previous [18] and present studies, we showed that the nature of the bread consumed has an impact on glucose, insulin, and incretin responses, but the mechanism is complex and requires further investigation.

To our knowledge, this is the first study to compare postprandial responses to ingestion of various breads delivering an identical amount of available CHO (thus different

masses) with the postprandial effect of ingestion of a fixed portion size (thus same volume, but different amounts of available CHO) of the same breads in overweight/obese men. It appears that bread volume and fiber content may play a role but are not the dominant factors in determining the metabolic responses to the breads, as in part 2 of the study, 11-grain, sprouted-grain, and 12-grain breads, with similar volume and fiber content, induced different results in almost every measure. These results suggest that the nature of the ingredients is an important factor influencing the metabolic responses to the breads. Lack of difference between 11-grain and white breads was unexpected but it may be that any positive impact of 11-grain on glucose metabolism only occurs after a chronic dietary intervention.

5. Conclusion

While the study is limited due to its applied nature (i.e., employing commercial breads and a somewhat heterogeneous subject set), this is also a strength in terms of applying the findings to the lifestyle of society. Despite the variation that these factors produced, the investigation demonstrated that sprouted grain bread attenuated the glycemic response when both portion size and available carbohydrate were controlled for and that, generally, the whole-grain breads did not have what could be interpreted as beneficial, metabolic responses.

Disclosure

At the time of research completion, all authors were affiliated with the Department of Human Health and Nutritional Sciences, University of Guelph, Canada.

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Review Article

Present Status and Perspectives on the Use of Alkylresorcinols as Biomarkers of Wholegrain Wheat and Rye Intake

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Alkylresorcinols (ARs) were first proposed as potential biomarkers of wholegrain wheat and rye intake a decade ago. Since then there has been a considerable body of research which suggests that ARs do meet most criteria of a biomarker of these foods. Results from human studies on plasma AR and their plasma and urinary metabolites strongly indicate that these compounds are responsive to whole grain wheat and rye intake and are correlated with various measures of AR consumption. This review briefly summarises work on the bioactivities of AR and focuses on aspects related to their use as biomarkers of whole grain wheat and rye intake. Evidence suggests that they thus far broadly fulfil the criteria to act as biomarkers of these cereals. However, there are still gaps in the knowledge on factors relating to the wide interindividual variation, and application to different epidemiological cohorts. Overall, ARs are highly promising biomarkers of whole grain wheat and rye intake and add to our increasing understanding of whole grains and health.

1. Introduction

Many epidemiological studies link a greater intake of wholegrain (WG) cereals to a decreased risk of many diet-related diseases including cardiovascular disease, obesity, type 2 diabetes, and some types of cancer [1–4]. In nutritional epidemiology, collecting valid dietary intake data, especially with food frequency questionnaires (FFQs), is challenging and remains one of the main weaknesses of this type of research [5]. For estimating WG intake, there are a number of additional challenges, including the breadth of different foods and processing methods this food category covers, and the difficulty that consumers (and researchers) have in accurately knowing the WG content of foods consumed [6]. One way of ameliorating this uncertainty around assessment of WG intake would be to use biomarkers of WG intake in conjunction with dietary assessment, and perhaps ultimately without dietary assessment (e.g., in cohorts where dietary data is not available or of questionable reliability such as blood banks and the elderly) to provide a nonsubjective estimate of intake [7]. Biomarkers of WG intake could also be of use as markers of compliance in long-term intervention studies that are being carried out in order to establish causality between increased WG intake and decreased risk of disease.

In the early part of this century, alkylresorcinols (ARs) were proposed as potential biomarkers of wholegrain wheat and rye intake [8]. ARs are 3,5-dihydroxy-phenolic lipids with an odd-numbered alkyl chain generally ranging from C15 to C25, and among food plants, only found in appreciable quantities in wheat, rye, barley, and triticale (a wheat × rye hybrid) [9] (Figure 1). The alkyl chains are mostly saturated (>80%) [9], though unsaturated, keto, and oxo-derivatives are also found, particularly in rye [10–12]. In the kernels, ARs are only found in the inner pericarp, hyaline layer, and testa [13], meaning that in food they are only present in the wholegrain or bran fraction of these cereals. The ratio of the different saturated homologues differs between the different cereals and can be used to differentiate between the three main ARs containing cereals [14] (Figure 2). The ratio of C17 : 0/C21 : 0 is approximately 0.1 in wheat (0.01 for durum wheat) and 1 in rye, and this ratio has been suggested to be a method for determining if a cereal product contains wheat, rye, or a mixture [14, 15] (Table 1). Barley has a much larger proportion of C25 : 0 compared to the other cereals, though overall has much

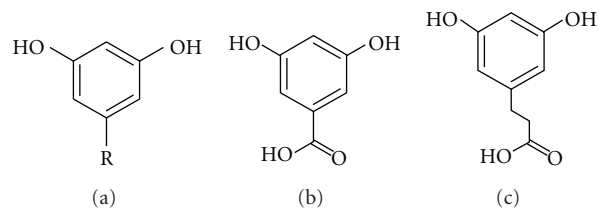

Figure 1: Basic structure of alkylresorcinols (a), and the two main plasma and urinary metabolites, 3,5-dihydroxybenzoic acid (b), and 3,5-dihydroxyphenylpropianoic acid (c). For the most abundant alkylresorcinols in cereals, R = $C_{17}H_{35}$–$C_{25}H_{51}$.

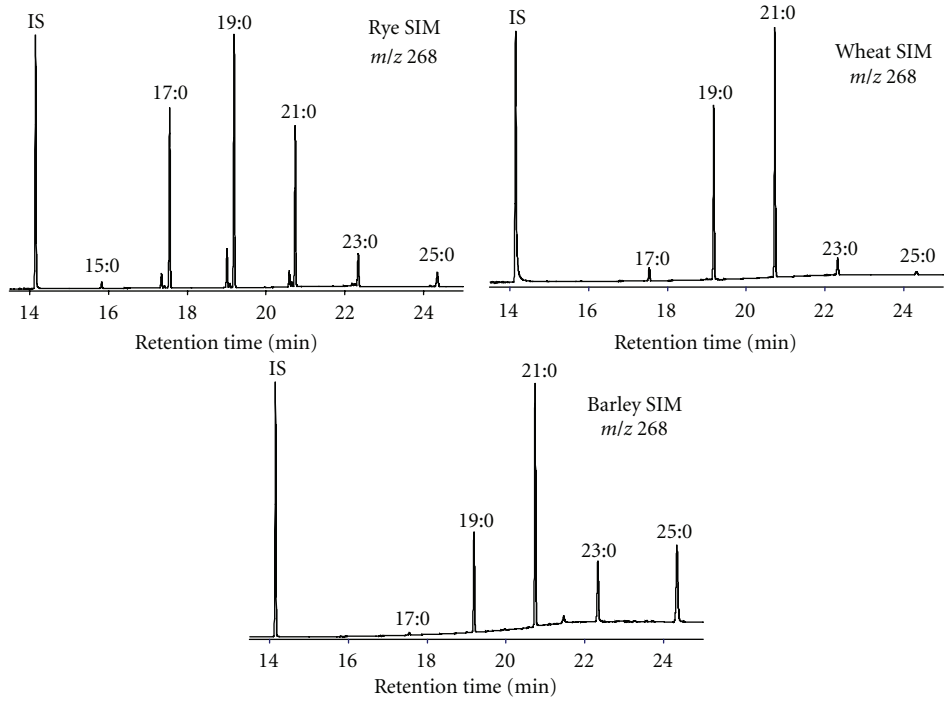

Figure 2: GC-MS chromatograms of the main AR containing cereals: wheat, rye, and barley. The ratio of the different odd-numbered saturated homologues varies from grain to grain but is generally conserved from variety to variety. The ratio C17 : 0/C21 : 0 can be used to determine if a cereal sample is wheat (~0.1) or rye (~1.0) and is reflected partially in plasma.

lower total AR concentrations (40–110 μg/g versus 300–1500 μg/g for wheat and rye) [9, 16–18]. ARs are not found in appreciable concentrations in other food plants, though homologues C15 : 0, C17 : 1, and C17 : 2 have been found in mango flesh at low concentrations (4–17 mg/kg fresh weight) [19]. Estimates for average daily intake range from 12 mg in the United Kingdom to nearly 40 mg in Finland [20], though this may underestimate intakes at the low end of the range as the small amounts present in white wheat flour were not accounted for [16].

2. Bioactivity of Alkylresorcinols

Current evidence for an important bioactivity of ARs is mostly weak and based on in vitro tests, with likely activity revolving around their ability to integrate into membranes and inhibit enzymes [21]. A wide variety of bioactivities have been ascribed to AR from in vitro tests, ranging from induction of apoptosis, inhibition of lipoxygenases, and cleavage of DNA to triglyceride reduction in adipocytes [8, 12, 21, 22]. The range of effective concentrations (based on reported IC_{50}) is around 3–100 μmol/L. Here it is important to note that the C_{max} of plasma alkylresorcinols after a single meal containing 190 mg of rye AR was 3-4 μmol/L [23], meaning that likely plasma concentrations are unlikely to reach a point where acute effects could be observed at "normal" intakes of 12–40 mg/d. The maximum AR concentration found in a small sample of human adipose tissues was 3.8 μmol/kg [24], suggesting that AR could possibly accumulate in some tissues to relatively high concentrations and play some biological role, though significant in vitro effects on lipolysis in adipocytes were only observed at 34–38 μmol/L [22].

ARs do have some antioxidant capacity, but this is weak compared to known antioxidants such as α-tocopherol [25, 26]. They were found to have slight antimutagenic and better antioxidant effects in membrane-based models [26]. The concentration needed to observe the inhibition

Table 1: Key steps for validating a biomarker, and if alkylresorcinols meet these criteria as biomarkers of alkylresorcinol containing foods (adapted from [75, 82]).

(1) Present in wholegrain foods, but not refined foods, nor other food sources		
Quantitative analytical methods for grains and food	GC	[9, 83]
	HPLC	[16, 84, 85]
	Colorimetry	[86–88]
Not present in other foods	In food plants, only found in wheat, rye and barley, and genetically related crops, and in low amounts in mango flesh. Very low amounts in beer and animal fat.	[9, 19, 70]
Not affected by food processing	AR stable during baking and pasta production	[9, 15]
	Limited effect of fermentation and germination in rye	[89, 90]
Variation in raw material	Wheat (350–900 μg/g)	[9, 15, 91, 92]
	Rye (500–1300 μg/g)	[83, 93, 94]
	Barley (30–100 μg/g)	[17, 18]
(2) Intake, absorption, distribution, metabolism, and elimination		
Quantitative analytical methods for biological samples	GC-MS (plasma, erythrocytes, adipose tissue, urinary metabolites)	[41, 55, 57] [46, 59]
	GC-MS/MS (plasma, erythrocytes)	[58]
	LC-MS/MS (plasma)	[56]
	HPLC-CAED (metabolites)	[48, 49]
Intake	Average intake in the UK and Sweden estimated to be 12 and 23 mg/d, respectively	[20]
Absorption	Pigs: 60–79% depending on dose	[44]
	Humans: 58% ileal absorption	[43]
Distribution	Rats: negligible accumulation 100 h after a single dose	[44]
	Adipose: AR-measured in rat and human adipose	[29, 46]
Metabolism	Main AR metabolites in humans: DHBA and DHPPA	[47]
	DHBA and DHPPA also measured in human plasma	[49]
	DHPPA extensively glucuronidated in human urine	[59]
Elimination	61% and 31% of a single dose eliminated in faeces and urine in rats	[44]
	Urinary recovery 45–89% depending on dose	[45]
(3) Dose response and pharmacokinetics		
Dose response	Increased dose of AR leads to decreased absorption in pigs	[44]
	Urinary recovery % lower with increased AR dose	[45]
Pharmacokinetics	Pigs: T_{max}: 3 h; $T_{1/2}$: 4 h	[50]
	Humans: T_{max1}: 2.8 h; T_{max2}: 6.7 h; $T_{1/2}$: 4.8 h	[23]
	Plasma metabolites: T_{max}: 6 h; $T_{1/2}$: 10–16 h Urinary metabolites: T_{max}: 6 h; $T_{1/2}$: 10–12 h	[52, 53]
(4) Determinants of biological concentrations, variation, and reproducibility		
Determinants of plasma alkylresorcinol concentration	Gender: males have generally higher concentrations	[62, 63]
	Triglycerides and lipoproteins	[27, 63]
	Nonesterified fatty acids	[63]
Variation in different populations	Healthy subjects, fasting plasma	
	Mixed results for females with hormone-related cancers	[37, 70]
Reproducibility and validity	Intervention studies: good-to-moderate ICC	[54, 63]
	Free-living studies: low ICC	[62]
(5) Application in clinical and epidemiological studies		
Surrogate endpoint for WG intake	Endometrial cancer case-control study: no difference in nonfasting plasma AR	[38]
Validation of dietary assessment tools	WG FFQ: correlation with FFQ: 0.53	[76]
Biomarker of compliance to an intervention	WG interventions	[51, 63, 74]

of LDL oxidation was 2.5 μmol/L and 75 μmol/L to observe antimutagenic effects [26], whereas the average AR concentration in erythrocytes after an AR-rich diet was 315 nmol/L packed cells, and 166 nmol/L plasma in total lipoproteins [27], suggesting that strongly bioactive concentrations are unlikely in blood under normal conditions.

Only limited in vivo work has been carried out on the possible biological function of AR, with one study demonstrating that, at up to 5 g/kg feed, there is no toxic effect [28], and another demonstrated that AR could increase tissue γ-tocopherol concentrations via competitive inhibition of its metabolism by CYP450 enzymes [29]. Oral dosing with pure AR has not been tested in humans. While most evidence does not point to a strong bioactivity of AR, there is an increasing amount of in vitro and animal work that suggests that AR may play a role in preventing intestinal cancers. Recent studies suggest that AR are one of the main active components in the prevention of colon cancer by wheat bran and wheat bran oil in mouse and in vitro models [30–32], which is supported by previous evidence suggesting that cereal ARs have some antimutagenic and apoptotic activity [33–35], implying a mechanism for colon cancer prevention beyond fibre. This may not be the case for all types/stages of cancer, and purified AR had no effect on implanted prostate cancers in mice although rye bran did inhibit tumour growth in the same model [36]. A small case-control study with subjects with breast cancer found that plasma and urinary AR metabolites were lower in patients with breast cancer though cereal fibre intake was also lower, and it is not possible to imply causality [37]. In a larger case-control study, plasma AR did not predict lower endometrial cancer risk in Danish women [38] though, for both types of hormone-related cancers, there is no strong link between incidence and consumption of wholegrains.

3. Alkylresorcinols as Markers of Wholegrain Cereals in Food

ARs have been suggested to be potential markers for WG wheat and rye in food products [14] and have been used in multianalyte methods for determining the presence of difference cereal fractions in cereal foods, with AR being most indicative of the inner pericarp and testa [39, 40]. AR could also be used as a method for checking contamination of nongluten containing cereals with gluten containing cereals (wheat, rye, and barley). Even white flour contains low amounts of AR (20–50 μg/g; [16]), meaning that sufficiently sensitive methods (e.g., gas chromatography-mass spectrometry (GC-MS) or high-performance liquid chromatography coupled to either CoulArray electrochemical detection (HPLC-CAED) or fluorescence detection) could be suitable for this purpose. Similarly, plasma AR could be used as a method to check for the compliance of people with coeliac disease to coeliac-free diets, as even people following WG-free diets have low plasma AR concentrations, while people avoiding all gluten containing cereals have no AR present in their plasma [41].

4. Alkylresorcinols as Biomarkers of Wholegrain Wheat and Rye Intake

The general criteria for an intake biomarker and how well AR meet these are outlined in Table 1. As saturated ARs are only found in the outer parts of WG wheatrye, barley, and triticale, and not in other food plants, they are good potential biomarkers of these cereals (they can also be markers for the bran intake, though generally bran alone is consumed in much lower quantities than the wholegrain and is not included in the American Association of Cereal Chemist's wholegrain definition [42]). In addition, ARs are not destroyed during food processing [9, 15] and are well absorbed in humans [43] though data from pigs and humans suggests that the percentage absorption is lower at higher doses [44, 45]. After absorption, ARs are transported in lipoproteins (mostly HDL) [27] and may be distributed and stored in some tissues, especially adipose tissue [29, 46]. ARs are metabolised via β-oxidation of the alkyl chain into two main metabolites: DHPPA and DHBA [47]. These metabolites can be measured in plasma and urine and are also being assessed as biomarkers of wholegrain intake [48, 49].

Kinetic considerations are important in assessing if a biomarker could be a short, medium, or long-term indicator of dietary exposure. The half-life of AR in plasma is around 5 h [23] though the exact shape of the curve may differ against a background of regular AR intake compared to a single dose after a washout [50, 51]. For the two main AR metabolites, the estimated half-life is 10–16 h in plasma [52] and 10–12 h in urine [53] though the dose used (100 mg total AR) is far greater than what would be expected for even a single day consuming WG-rich foods [20]. Landberg et al. [45] found in a dose-response study that increasing doses of AR lead to lower recoveries of AR metabolites in urine (89–45% between 22.5 and 90 mg AR/d), agreeing with previous data from pigs [44] that an increased intake does impact on absorption and metabolism, and that AR response in biological fluids may not be linear, especially at higher intakes (Figure 3). Fasting ARs do increase with regular intake, but also rapidly decrease with decreased or no intake (e.g., [27, 51, 54]; Figure 4), so that irregular intake of WG food would potentially be an important confounding factor though as cereal-based foods are generally part of the staple diet, their intake tends to be regular. One possibility for the use of AR as long-term biomarkers of WG intake is their analysis in adipose tissue [46]. While it is not known how important this pool is, nor the factors governing its turnover, it could be of use in studies where adipose tissue biopsy samples are available.

4.1. Methodological Considerations. ARs have been quantified in biological samples using a variety of methods. In plasma, they have been analysed using GC-MS [41, 55] and liquid chromatography-tandem mass spectrometry (LC-MS/MS) [56], erythrocytes using GC-MS [57] and GC-MS/MS [58], and in adipose tissue using GC-MS [24]. The two AR metabolites have been analysed in urine using GC-MS [47, 59] and in both plasma and urine using HPLC-CAED [48, 49]. In urine, the HPLC-CAED and GC-MS

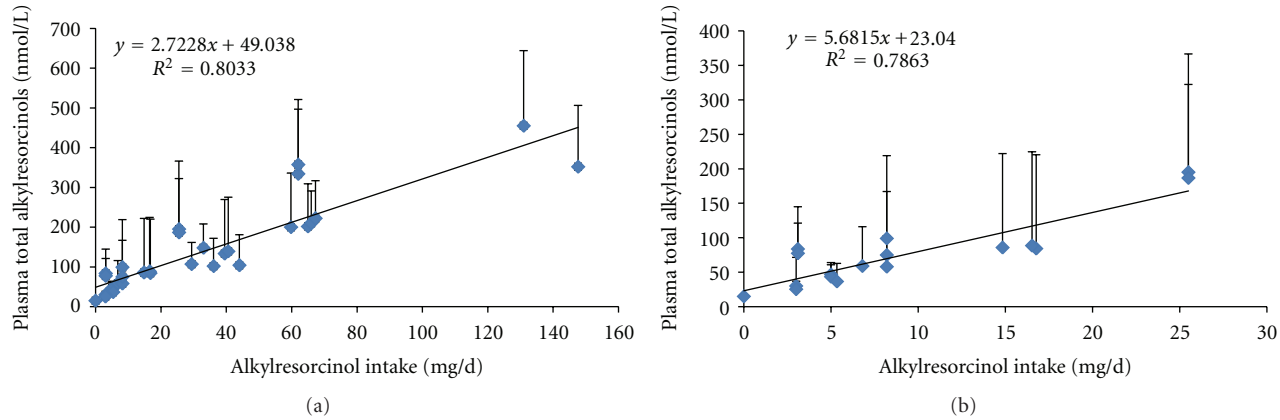

Figure 3: Relationship between mean AR intake and the mean of plasma AR across published studies (a). Where direct AR intake data was not provided, it was estimated from literature values if possible. Values are arithmetic means, and error bars are the standard deviation. Figure (b) uses data from studies where there has been an arm/group with an AR intake equivalent to 0–48 g of WG wheat (0–27 mg AR/d) to give an idea of the range at "normal" intakes, as well as the likely intercept for no WG intake.

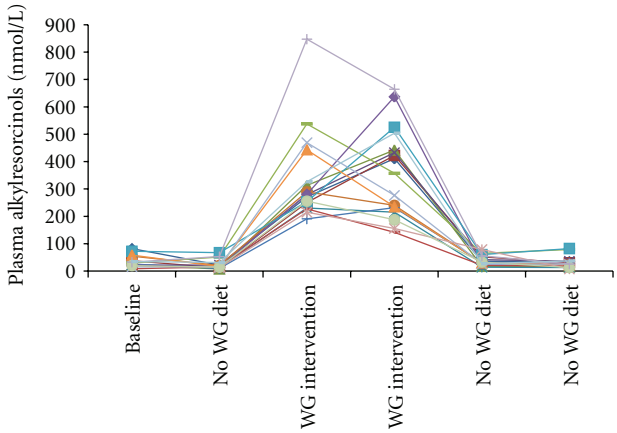

Figure 4: An example of interindividual variation of plasma alkylresorcinols under controlled conditions. The wholegrain intervention delivered approximately 62 mg alkylresorcinols/d. Each time point is one week apart. Data are from [51].

give comparable results [60]. Due to the relatively low concentrations present in plasma, MS-based methods are needed for the intact AR. GC-MS has been the main instrument used though this requires liquid-liquid extraction followed by solid phase extraction cleanup and derivitasation compared to only liquid-liquid extraction and centrifugation for normal-phase LC-MS/MS. For both methods, run times are similar (15–20 minutes injection to injection) though GC-MS has marginally greater sensitivity. MS also has the advantage that labelled internal standards can be used that are less prone to contamination or peak-overlapping issues than other types of internal standard. The use of the cheaper HPLC-CAED for analysis of metabolites for large cohorts of samples is attractive but needs to be balanced against a longer sample preparation as samples need to be deconjugated overnight, and liquid-liquid extraction is still required for plasma samples. A longer chromatographic separation and reequilibration time is needed (60 minutes per sample), greatly reducing throughput, and there is the potential for overlapping peaks; paracetamol/acetaminophen has been found to coelute with DHBA [61]. Additionally there is no information on if wheat or rye was the main source of wholegrain, if this is of interest. Ultimately antibody-based assays or similar methods will be required for AR/AR metabolite analysis to be routine in large epidemiological cohorts.

4.2. Studies Using AR as a Biomarker

4.2.1. Intervention Studies. ARs have now been measured in a number of intervention studies which now allows an overview of their performance under a variety of conditions. All studies have found that plasma AR and AR metabolites in plasma and urine are generally responsive to increased WG wheat/rye intake and that concentrations decrease rapidly on WG-free diets. The published studies are summarised in Figures 4 and 5, and Tables 2 and 3. While on average plasma ARs are highly responsive to the consumption of foods containing AR, there is a wide range of interindividual variation. Landberg et al. [54] found that repeatability, as determined using the intraclass correlation coefficient, was good under intervention conditions (ICC = 0.88 – 0.9), but less so under free-living conditions (ICC = 0.42–0.48, with one study finding a large difference between men and women) [62–64]. This variation in free-living subjects does make it difficult to classify an individual's WG wheat/rye intake with great precision based on a single sample though currently it appears as though it is a valid measure for comparing different populations, as mean plasma ARs are well correlated with mean AR intake when results from relevant studies are combined (Figure 3).

4.2.2. Correlation of AR in Biological Fluids with Measurements of Wholegrain Intake. Correlations between plasma AR and various measures of their intake (AR intake, WG intake, cereal fibre intake) range between 0.25 and 0.58

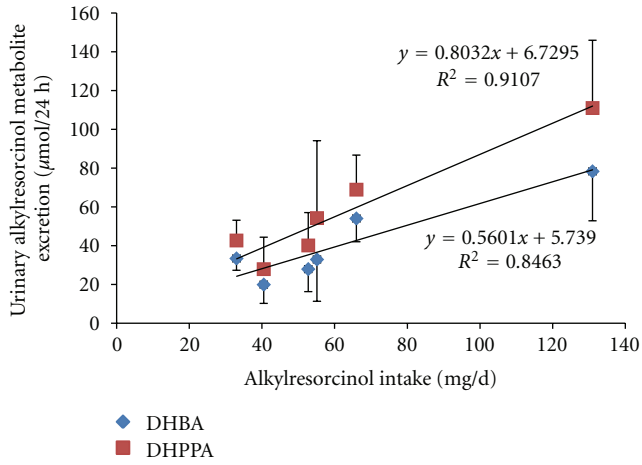

Figure 5: Relationship between mean AR intake and the mean of urinary AR from three published studies. Where direct AR intake data was not provided, it was estimated from literature values if possible. Values are arithmetic means, and error bars are the standard deviation.

(Table 2), with generally better correlations with more detailed dietary intake instruments. The studies using a general diet FFQ had the lowest correlations (<0.4), with food diaries between 0.32 and 0.52, and weighed food records and specific WG FFQ between 0.5 and 0.58. This fits with the assumption that general dietary recording methods such as FFQ are not the best instruments for collecting data on WG intake. The correlations found for plasma and urinary AR metabolites are in a similar range to the intact compounds (Table 3). While measuring urinary metabolites has an advantage over plasma samples as they are relatively unaffected by fluctuations due to different meal times (provided they are 12 or 24 h collections [65], presently there does not appear to be an advantage for either AR or their metabolites, and the metabolites are yet to be assessed in larger populations (>100 subjects) and at lower levels of AR intake (Figure 5). In the one study where the two have been compared, there were no major differences between total plasma AR or urinary AR metabolites [66]. The type of dietary exposure measurement related to AR/AR metabolite response surprisingly does not appear to be of great importance, as even very broad categories such as WG intake or rye intake lead to similar correlations to AR intake. One exception is in an intervention study based in the UK, where many subjects had low WG intake, but still varied in AR intake due to a high consumption of refined wheat foods, and correlation with AR intake was somewhat better than with WG intake (Table 2) [63].

Correlations for AR and AR metabolites are generally higher than those for α-carotene, β-cryptoxanthin, and lycopene for consumption of vegetables, fruits, and tomatoes, respectively [67, 68], and as in the case of fruits and vegetables, the choice of dietary recall method is important. Correlations could be improved by the use of absorption estimates to improve the association with estimated intake and plasma AR. Absorption estimates improved validity coefficients for serum lycopene determined using the method of triads by 50% and 100% for lycopene intake determined by 3DWFR [69]. Limited human absorption and bioavailability data exist for AR [23, 43, 45], and these studies have generally used intakes well beyond what would be expected in the general population, and more studies of this nature will be invaluable for improving the estimation of WG intake via plasma AR.

4.2.3. Application of Alkylresorcinols as Surrogate Measurements of WG Intake in Epidemiological Studies. To date, only one study has used AR as a surrogate marker of WG intake. This study did not find a relationship between plasma AR and endometrial cancer incidence [38] but did find that nonfasting plasma AR and rye bread intake were moderately correlated ($r = 0.25$) [70]. This study specifically used plasma AR measurements in an attempt to improve the estimation of WG intake in this cohort. As this study used nonfasting plasma samples, there may have been greater variation, making it potentially more difficult to find associations, even when time since last meal is accounted for. The half life of AR is relatively short [23], and a single consumption event is unlikely to have a major impact on overnight fasting plasma AR concentrations but could do on a nonfasting sample. Andersson et al. found that the use of nonfasting samples leads to poor reproducibility (ICC = 0.18) [64], suggesting that they may not be ideal samples for using AR as biomarkers of WG intake. In this respect, more work is needed to compare the validity of fasting versus nonfasting plasma samples.

4.2.4. Alkylresorcinols as Biomarkers of Compliance. Dietary compliance is often uncertain in dietary intervention studies; particularly, free-living studies run over long periods of time. Compliance biomarkers are sometimes used in nutrition intervention studies to support diet record collection, though often these biomarkers are directly related to health outcomes or nutrient status, for example, plasma carotenoids, lipids, and 24 h urinary nitrogen and potassium [71–73]. Compliance biomarkers not only provide an additional control of dietary compliance but can be an additional motivating factor for subjects to comply, if they know that this will be checked in their biological samples.

Plasma ARs have only been used as a compliance biomarker in a few studies to date [51, 74]. One reason for this is that there is still uncertainty around cut-off points for determining when a person has not been eating a certain quantity of WG per day, or if they are naturally low absorbers/fast metabolisers of AR. Without clear criteria for determining compliance, it is difficult to exclude subjects on the basis of AR measurements, if traditional measurements indicate that they are compliant. At the population level, it appears as though it is not difficult to distinguish between 0-1 servings of WG versus 3 servings of WG (e.g., Figure 3) using plasma AR; at an individual level, it is questionable due to the great amount of interindividual variation. Table 4 lists the means and where possible the ranges for total plasma AR for nonwholegrain or low WG diets in the literature to date. Mean concentrations range from 33 to 84 nmol/L though,

Table 2: Correlations of plasma alkylresorcinol concentration with different measurements of wholegrain intake from previously published studies.

N	Gender	Country	Type of study	Dietary assessment method	Dietary exposure parameter	Correlation	*P* value	C17 : 0/C21 : 0	Reference
39	F[a]	Finland	Intervention	4DFR[b]	Rye bread intake	0.34	0.037	0.84	[95]
39	F	Finland	Intervention	4DFR	Insoluble fibre	0.39	0.013	0.84	[95]
28	F+M	Sweden	Intervention	3DFR[c]	AR	0.58	<0.001	0.30	[77]
56	F	Finland	Free-living	5DFR[d]	Cereal fibre	0.38	0.004	0.62	[66]
29	F+M	Switzerland	Free-living	3DWFR[e]	WG intake	0.57	<0.001	0.17	[76]
29	F+M	Switzerland	Free-living	WG FFQ[f]	WG intake	0.55	<0.001	0.17	[76]
360	F	Denmark	Prospective	FFQ[g]	Rye bread intake	0.25	<0.001	0.40	[70]
266	F+M	UK	Intervention	FFQ	WG intake	0.35[i]	<0.001	0.07	[63]
266	F+M	UK	Intervention	FFQ	WW[h] intake	0.43[i]	<0.001	0.07	[63]
266	F+M	UK	Intervention	FFQ	AR intake	0.39[i]	<0.001	0.07	[63]

[a]F: female, M: male
[b]4DFR: 4-day food record
[c]3DFR: 3-day food record
[d]5DFR: 5-day food record
[e]3DWFD: 3-day weighed food diary
[f]WG-FFQ: Wholegrain food frequency questionnaire
[g]General diet food frequency questionnaire
[h]WW: Wholegrain wheat
[i]After 16-week intervention.

Table 3: Correlations of plasma and urinary alkylresorcinol metabolites (DHBA and DHPPA) with different measurements of wholegrain intake from previously published studies.

N	Gender	Country	Type of study	Dietary assessment method	Diet exposure parameter	AR metabolite	Plasma/urine	Correlation	*P* value	Reference
56	F[a]	Finland	Free-living	5DFR[b]	Cereal fibre	DHBA[c]	24 h urine	0.37	0.005	[66]
56	F	Finland	Free-living	5DFR	Cereal fibre	DHPPA[d]	24 h urine	0.41	0.002	[66]
56	F	Finland	Free-living	5DFR	Cereal fibre	DHBA	Plasma	0.41	<0.01	[96]
56	F	Finland	Free-living	5DFR	Cereal fibre	DHPPA	Plasma	0.46	<0.01	[96]
56	F	Finland	Free-living	5DFR	Cereal fibre	Total AR metabolites	Plasma	0.42	<0.01	[96]
60	F	Finland	Free-living	5DFR	Rye	DHBA	Plasma	0.32	<0.05	[97]
60	F	Finland	Free-living	5DFR	Rye	DHPPA	Plasma	0.39	<0.01	[97]
60	F	Finland	Free-living	5DFR	Rye	Total AR metabolites	Plasma	0.33	<0.05	[97]
60	F	Finland	Free-living	5DFR	Rye	DHBA	24 h urine	0.52	<0.001	[97]
60	F	Finland	Free-living	5DFR	Rye	DHPPA	24 h urine	0.44	<0.001	[97]
60	F	Finland	Free-living	5DFR	Rye	Total AR metabolites	24 h urine	0.48	<0.001	[97]

[a]F: female
[b]5DFR: 5-day food record
[c]DHBA: 3,5-dihydroxybenzoic acid
[d]DHPPA: 3,5-dihydroxyphenylpropionoic acid.

when reported, the median is often much lower than the arithmetic mean, indicating that often the mean is skewed by relatively few high concentrations, resulting in high-standard deviations. Assessing the studies with the greatest dietary control (subjects instructed to avoid other cereal foods), as well as the skewness of the data (median versus mean) and the standard deviation, it would appear that someone with a plasma AR concentration >100 nmol/L is probably eating at least some WG in their diet, and, conversely, if a subject has a plasma AR concentration of <60–70 nmol/L, then they are probably not eating any WG in the diet. By plotting the studies that have recorded low intakes of AR (<30 mg/d), a diet free of cereal AR would lead to a mean plasma AR concentration of 31 nmol/L (Figure 3(b)). There is a great need for controlled studies which will allow the determination of realistic ranges for people eating no or less

Table 4: Plasma AR concentrations when subjects have consumed low or essentially AR-free diets.

N	Gender	Country	AR intake (mg/d)	Intervention type	Duration of intervention period (weeks)	Median	Mean	SD	Range	Reference
39	F[a]	FI	5.34[b]	Replace all bread with intervention breads	8		36.6	26.2	10.9–55.8[c]	[95]
15	F+M	FI	3[b]	Replace all bread with intervention breads	1		25–30	12–41	5.5–171	[27]
28	F+M	SE	6.8	All cereal foods provided	6		59	57	9–220	[77]
17	M	SE	8.2	Replace all cereal foods	6	33	72	101	17–410	[54]
17	F+M	CH	5	Fully controlled diet	2	40	44	17	27–89	[51]
34	F	DK	3.1[d]	Replace part of cereals in diet	12	61	78	43.7	16–246	[74]
266	F+M	UK	17	WG consumption < 30 g/d	0	69.5	84.3	136	10–875	[63]
16	F+M	SE	WG-free diet	Avoid all WG foods	1		60–68	33–37	23–178	[45]
17	F+M	CH	WG-free diet	Avoid all WG foods	1	19–32	25–38	13–21	7–82	[51]

[a] F: female, M: male
[b] Estimated intake from refined wheat bread intake
[c] Excludes outliers
[d] Amount provided by intervention, not total diet.

than one serving of wholegrain per day, and to determine at what amount of wholegrain intake is it possible to say that they are categorically complying with the diet.

4.2.5. Response of AR and AR Metabolites in Biological Fluids after Interventions. Using effect size estimates, it is possible to estimate the average response of plasma AR to a given amount of AR or WG intake. Landberg et al. [70] estimated that plasma AR would increase on average by 85 nmol/L for every 100 g of rye bread eaten in a Danish population, equating to an increase of 85 nmol/L for every 70 mg of AR consumed (based on 700 μg AR/g for Danish rye bread [9, 16]). In a UK intervention study, it was estimated that 10 g of WG would lead to a 6% increase in plasma AR [63].

4.2.6. Use of the Alkylresorcinol Homologue Ratios in Biological Samples. The ratio of the homologues C17 : 0 and C21 : 0 is indicative of wheat or rye in cereal samples, and this has been found to be reflected to some extent in human samples [27] although the ratio after a rye diet is a lot less than 1—usually around 0.3. This is presumed to be due to the faster metabolism of the longer chain AR [23]. In populations where both wheat and rye are eaten, it could be possible to use the C17 : 0/C21 : 0 ratio to determine if a person eats more of one of these cereals than the other. Presently there has been little specific research on the use of this ratio to determine the source of the cereal in the diet though it is clearly different between wheat-based and rye-based interventions. As the ratio in wheat is never above 0.1, it would theoretically be impossible for a subject just eating wheat to have a ratio above 0.1, so that any ratio above this in plasma would indicate at least some rye in the diet. However, this can be confounded at low concentration levels as C17 : 0, a minor homologue in wheat, may be close to the limit of quantification in plasma. In studies in populations that have rye as an important source of wholegrain, where AR concentrations have been measured (i.e., Denmark, Finland and Sweden), the ratio is generally above 0.1 [75]. However, in those populations where rye is not commonly consumed, the ratios are generally lower: 0.17 ± 0.14 for Switzerland [76], 0.06 after a 16-week WG-based intervention in the UK [63], and 0.08 ± 0.06 after a 12-week WG wheat intervention in Danish women [74] (Table 2). Together these results suggest that the C17 : 0/C21 : 0 ratio should be indicative of the source of AR beyond intervention studies and that ratios above 0.15 are probably indicative of rye intake, provided that potential analytical errors are accounted for. More understanding of the absorption and metabolism of the different homologues is required for more accurate use of the C17 : 0/C21 : 0 ratio for determining the source of AR.

4.2.7. Noncereal Determinants of Plasma Alkylresorcinol Concentration. While the wide interindividual variation of plasma AR concentrations with similar intakes is well established (e.g., [51, 77]), there is still little information about what additional factors influence AR concentrations in plasma, and their metabolism. Two studies have found differences in concentrations between males and females [62, 63], but no such consistent effects have been found for age or BMI [62, 63, 70]. Under intervention conditions, while mean AR concentrations were different between the genders, the ability of AR to distinguish between different intake levels was similar [63], but ICC estimated for free-living Germans was very different, with females having much higher ICC for repeated plasma AR measurements than males [62]. Plasma lipids are correlated with plasma AR, though whether this is an independent determinant is debatable, as two studies have found that adjusting for total plasma lipids has had

little or no effect on correlations with measures of AR intake [63, 70]. As ARs do not appear to play a particular role in vital bodily functions, it is unlikely that there are specific control mechanisms that would exert homeostatic control over AR concentrations in plasma or excretion in urine.

4.2.8. Application of Biological Measurements of Alkylresorcinols for Dietary Recall Method Validation. While in some cases measurements of AR or AR metabolites could be used where dietary intake data does not exist or is not well suited for determining WG intake, the true potential of measuring AR in epidemiological studies lies in improving estimations of WG intake. Examples of this are the calibration of dietary recall methods, and to identify likely under- or overreporters of intake [78]. The method of triads is a widely used tool to calibrate new dietary questionnaires, using a "gold standard" method (e.g., weighed food record or 24 h recall), the questionnaire being tested, and a biomarker [79]. Because the measurement errors for the two subjective methods are correlated, the biomarker provides a crucial unbiased measurement of intake [80]. In a small study ($n = 29$) [76], the validity coefficients (a measure of "closeness" to estimated true intake) was 0.65 for plasma AR (Ross et al. unpublished observations), though larger numbers of subjects (e.g., >100) would be needed to strengthen this observation. Estimation of how well AR or AR metabolite measurements classify or rank subjects according to intake is also important to gauge their validity as biomarkers of intake [81] to know if they can reliably distinguish between extremes of WG intake.

5. Notes for Using Alkylresorcinols in Clinical Trials

Researchers wishing to use AR as biomarkers of WG intake, either as a surrogate marker of intake, or as a check of compliance should bear in mind the following.

(i) Blood is best collected on EDTA—while no studies have directly compared EDTA versus other coagulants, generally EDTA provides better stability for lipophilic compounds.

(ii) If possible, collect cereal food samples associated with the study (if an intervention) or from the area where the study has been carried out, in order to get an estimate of AR intake. Some foods may differ from what might be expected.

(iii) If possible, keep some check on the time since last meal. Nonfasting samples are not recommended for estimating possible WG intake, and large differences in time since last meal between subjects or time points may have an impact on the results.

(iv) ARs are relatively responsive to changes in WG wheat/rye intake, and a one-week non-WG washout is sufficient to go from high plasma AR concentrations to low plasma AR concentrations.

6. Current Status and Gaps

Presently, ARs appear to be highly promising biomarkers of wholegrain wheat and rye though there are many factors that are poorly understood. Present studies find that intake of these grains still only accounts for 9–11% of the variation observed, even under relatively controlled conditions. This would suggest that unknown genetic or lifestyle factors play an even larger role in determining their concentration in individuals, even if the only dietary source is from these cereals. However, there is a strong correlation between mean concentrations and mean intake, suggesting that while ARs may be only moderate in predicting individual WG intake, they may strongly predict mean intake in larger populations.

Now that it is clear that plasma AR increases with greater WG intake, there is a need for more studies that look at the validity of AR as biomarkers at ranges of WG intake that are relevant to the intake that would be expected in general populations. More studies are also needed in non-European populations in order to assess their applicability across different types of WG intake.

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Review Article

Beta Glucan: Health Benefits in Obesity and Metabolic Syndrome

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Despite the lack of international agreement regarding the definition and classification of fiber, there is established evidence on the role of dietary fibers in obesity and metabolic syndrome. Beta glucan (β-glucan) is a soluble fiber readily available from oat and barley grains that has been gaining interest due to its multiple functional and bioactive properties. Its beneficial role in insulin resistance, dyslipidemia, hypertension, and obesity is being continuously documented. The fermentability of β-glucans and their ability to form highly viscous solutions in the human gut may constitute the basis of their health benefits. Consequently, the applicability of β-glucan as a food ingredient is being widely considered with the dual purposes of increasing the fiber content of food products and enhancing their health properties. Therefore, this paper explores the role of β-glucans in the prevention and treatment of characteristics of the metabolic syndrome, their underlying mechanisms of action, and their potential in food applications.

1. Introduction

Obesity has reached global epidemic proportions with more than one billion adults affected by this chronic disorder [1]. Coronary artery disease, stroke, insulin resistance, type 2 diabetes, hypertension, and metabolic syndrome are well-known medical comorbidities associated with excess body weight [2]. The metabolic syndrome is defined by a combination of three or more of the following: (a) abdominal circumference >102 cm (40″) for men and 88 cm (35″) for women, (b) hypertension, (c) hyperglycemia, and (d) dyslipidemia (elevated triacylglyceride concentrations and low levels of high-density lipoproteins (HDL) in blood) [3]. It is directly associated with increased risk of type 2 diabetes and cardiovascular diseases.

Many studies have examined the potential of diets and dietary components as a first-line intervention in the prevention and treatment of metabolic syndrome [4]. Accordingly, various dietary constituents, foods, and dietary practices, capable of controlling blood glucose, insulin and lipids, blood pressure, and food intake have been identified. Although the ideal dietary pattern for patients with metabolic syndrome has not been defined, there is growing evidence that high intakes of fruits, vegetables, legumes, and cereals are beneficial [5–11]. Many of their benefits have been attributed to their low-glycemic properties and their dietary fiber content. However, dietary fibers in fruits, vegetables, legumes, and cereals are poorly defined and vary greatly in characteristics.

The focus of this review is on beta glucan (β-glucan), which is a dietary fiber readily found in oat and barley bran. β-glucan is a relatively inexpensive milling byproduct, and it is added to foods on the assumption that this will contribute to health benefits. β-glucans are predominantly found in the internal aleurone and subaleurone cell walls [12–14]. The content of β-glucan varies with environmental conditions during endosperm development and is regulated by $(1 \rightarrow 3, 1 \rightarrow 4)$-$\beta$-glucan endohydrolase (EC 3.2.1.73 also known as licheninase or 1,3-1,4-beta glucanase) to facilitate endosperm cell-wall degradation during germination [15]. Among cereals, the highest content (g per 100 g dry weight) of β-glucan has been reported for barley: 2–20 g (65% is water-soluble fraction) and for oats: 3–8 g (82% is water-soluble fraction). Other cereals also contain β-glucan but in much lower amounts: sorghum 1.1–6.2 g, rye 1.3–2.7 g, maize 0.8–1.7 g, triticale 0.3–1.2 g, wheat 0.5–1.0 g, durum wheat 0.5-0.6 g, and rice 0.13 g [16]. Other sources of β-glucan include some types of seaweed [17] and various species of mushrooms such as Reishi, Shiitake, and Maitake [18].

Canada is a major producer of both oats and barley, producing 2297.6 and 7605.3 thousand metric tonnes of oats and barley, respectively, in 2010/2011 [19, 20]. In 2007, Canada was the 5th leading producer of barley and the 2nd leading producer of oats worldwide [21]. Fractions rich in β-glucans are readily obtained from cereal grains by dry milling followed by sieving and air classification processes or by wet milling followed by sieving and solvent extractions [22]. These approaches result in concentrates or isolates containing 8–30% and 95% β-glucans, respectively. During oat processing, oat bran and aleurone layers can be milled from oat groat, creating the bran as a major byproduct. Oat β-glucan is found in greater concentrations in the bran as compared to the whole-oat groat and commercial oat bran contains 7–10% β-glucan [23]. However, extraction of pure β-glucan isolates is not straightforward and relatively costly since the aleurone and subaleurone cell walls also enclose starch, protein, and lipids [24]. Thus, pure β-glucan isolates are often ignored in food product development and relatively inexpensive oat and barley bran or flour fractions are typically used.

The objective of the current review is to illustrate the role of β-glucan, as a soluble and fermentable fiber, in the prevention and treatment of various metabolic syndrome-linked diseases. β-glucan is then compared to other soluble and fermentable dietary fibers, clarifying whether the effects of β-glucan on health and disease are unique. An overview of definitions and types of fiber is provided first and then followed by an in-depth examination of the health benefits associated with β-glucan, its mechanisms of action, and its potential food applications.

2. Dietary Fibers: Characteristics, Definitions, Classifications, and Analytical Methods

Scientific and regulatory bodies around the world define fiber differently. The challenge of defining fiber is probably best exemplified by the 10-year process that was required to achieve an international legal definition for dietary fiber by Codex [25]. Most definitions of fiber address its biological, chemical, and nutritional characteristics while recent regulatory requirements have created the need for analytical definitions. Fibers can also be categorized based on their physical and chemical properties as well as their physiological effects. The following sections outline some characteristics of fiber, its various definitions and classifications as well as the analytical approaches used for its quantification. Prior to an in-depth examination of β-glucan, a brief overview describing the role of dietary fibers in metabolic syndrome will be given.

2.1. Characteristics of Dietary Fibers. Four categories of fiber definitions have been identified [26], each of which addresses a different characteristic of fiber. In general, these categories describe fiber based on its source, chemical composition, digestibility, metabolic fate, and physiological effects. Depending on which characteristic is used to define fiber, various carbohydrates can be included under the definition. Each category of definitions has its advantages and disadvantages and because of the variation in fiber types, a combination of different approaches is usually necessary in order to define fiber in a comprehensive manner.

Biological definitions describe the origins of fiber and have historically referred to nonstarch polysaccharides from plant cell walls. The earliest formal definition of fiber refers to the source of fiber: "Dietary fibre is the proportion of food which is derived from the cellular walls of plants, which is digested very poorly in human beings" [27]. This definition was soon updated to include nondigestible polysaccharides that are not part of the plant cell wall [28], in order to account for storage carbohydrates such as guar gum. However, this definition remains limiting as fibers can also be obtained from animal, fungal, bacterial, and synthetic sources. Categorization based on source is also complicated by the inability of analytical methods to distinguish fiber origin [29].

Chemically, fiber can be described based on its chain length and type of linkages between each monomeric unit. This provides a very precise and unequivocal meaning; however, deciding on the appropriate chain length for fiber has been difficult. The Codex definition for fiber indicates that fibers have a degree of polymerization (DP) $\geq$ 10, but also includes a footnote that the decision on whether to include carbohydrates with a DP > 2 (i.e., oligosaccharides) is up to national authorities [30]. Fibers can also be described based on the chemical bonds between their monomeric units as nonstarch polysaccharides are typically linked by β-linkages; however, this specification would exclude resistant starches, which contain α-1,4 linkages.

The physiological effects of fiber refer to its nondigestibility and metabolic effects. Nondigestibility in the small intestine is fundamental to fiber and was part of the first definition put forth by Trowell [27]. However, nondigestibility and a lack of absorption by the small intestine alone do not guarantee favourable physiological effects. Depending on physicochemical properties, fibers have a range of physiological consequences including viscosity in the upper gastrointestinal tract [31, 32], fermentation in the colon [33], and prebiotic effects [34, 35]. These effects in the gastrointestinal tract improve laxation and increase stool bulking and also have metabolic consequences including improvements in serum lipids and postprandial glycemia and promotion of satiety.

Analytical definitions are used for labelling and inspection purposes. They often describe an "official method," which is simple and reproducible enough to minimize dispute. The risk with these types of definitions is that they are not able to recognize new fiber compounds, which may have significant and beneficial health implications. Consequentially, the "official method" has to be continually updated to measure these new compounds. This type of definition is very practical from a regulatory point of view; however, it alone does not actually describe any characteristics of fiber and an analytical method should only be part of a formal regulatory definition.

2.2. Definitions of Dietary Fibers. The most recent definitions for fiber generally address at least one of four characteristics: (1) source, (2) chemical characteristics, (3) resistance to

digestion, and (4) beneficial biological effects. With the advances of food science, isolation, modification, and synthesis of many fibers are possible, which have resulted in some jurisdictions distinguishing between naturally occurring fibers from plant source and isolated or synthesized fibers. Others have chosen not to adopt this division by either considering all nondigestible carbohydrates as fiber or only those carbohydrates that are intrinsic and intact in plants. Table 1 lists examples of such definitions based on this division.

2.3. Classification of Dietary Fibers. As seen in the previous section, fibers are often classified by their source (plant, animal, isolated, synthetic, etc.), but they can also be classified according to chemical, physical, or physiological criteria [36, 37].

2.3.1. Chemical (Polymer Length and Types of Linkages). Chemical classification can divide carbohydrates based on their chain length, or DP: sugars (DP 1-2), oligosaccharides (DP 3–9), and polysaccharides (DP $\geq$ 10). Oligosaccharides are either (a) maltodextrins (α-glucans), principally resulting from the hydrolysis of starch, or (b) non-α-glucan such as raffinose and stachyose, fructo- and galactooligosaccharides and other oligosaccharides. Polysaccharides may be divided into starch (α-1,4 and 1,6 glucans) and nonstarch polysaccharides, which primarily consist of plant cell wall polysaccharides such as cellulose, hemicelluloses, and pectin but also includes plant gums, mucilages, and hydrocolloids. However, some carbohydrates do not fit into this categorization. For instance, inulin may have from 2 to 200 fructose units and thus can be both oligo- and polysaccharide [35].

2.3.2. Physical (Solubility and Viscosity). Fibers are most commonly characterized based on their solubility. Distinction between soluble and insoluble dietary fibers is based on the solubility characteristics of dietary fiber in hot aqueous buffer solutions [38]. Solubility of dietary fiber structure cannot be simply described as the solubility in water. Solubility of dietary fibers is rather defined as dissolved or liquefied in a buffer and enzyme solution modeled after, but not necessarily identical to, the aqueous enzyme solutions or slurries present in the human system [39]. Insoluble fibers primarily consist of cellulose and some hemicelluloses, resistant starch, and chitin while soluble fibers include pectins, β-glucans, galactomannan gums, mucilages, and some hemicelluloses. Solubility can be used as a means to broadly characterize the physiological effects of fibers. In general, insoluble fibers increase fecal bulk and the excretion of bile acids and decrease intestinal transit time (i.e., laxative effect). Soluble fibers increase total transit time by delaying gastric emptying and also slow glucose absorption [40]. Although this characterization of fiber is used to generalize the effects of each fiber type, only soluble viscous fibers delay gastric emptying time and slow glucose absorption while nonviscous soluble fibers primarily act as a substrate for microbial fermentation in the colon [33].

2.3.3. Physiological (Rate of Digestion and Fermentation). The rate at which a carbohydrate is digested is determined by a number of factors, including the rate at which carbohydrate leaves the stomach and becomes available for absorption as well as diffusion of released sugars occurs from food bolus [41]. Thus, the rate at which carbohydrates leave the food matrix and the ability for amylase to act on the carbohydrate is an important determinant of glucose absorption rate and resulting blood glucose levels. Based on digestion, carbohydrates can be categorized as rapidly or slowly digested or even resistant. Resistant carbohydrates include plant cell wall polysaccharides, gums, fructans, resistant maltodextrins, and resistant starches.

These carbohydrates that resist digestion make their way to the large intestine, where they may be fermented by the gut microflora [33] or have prebiotic effects [34]. However, not all fiber is fermented. Short-chained fatty acids produced from fermentation are mainly sourced from resistant starches [42, 43]. Insoluble fibers (e.g., lignins, cellulose, and some hemicelluloses) are resistant to fermentation while soluble fibers (e.g., pectins, gums, mucilages, and some hemicelluloses) are more completely fermented by colonic microflora [33]. A prebiotic is a nondigestible food ingredient that selectively stimulates the growth and/or activity of a limited number of colonic bacteria and subsequently improves host health [44]. Prebiotic fibers alter the balance of the gut microflora towards what is considered to be a healthier one [34] and includes fructans and resistant starches [45].

2.4. Analytical Methods for Fiber Quantification. For food labelling purposes, it is important that analytical methods complement the fiber definition in a given jurisdiction. Fibers are typically measured by enzymatic-gravimetric methods, although there are also gravimetric, nonenzymatic-gravimetric, and enzymatic chemical methods. High-performance liquid chromatography (HPLC), gas liquid chromatography (GLC), and ion-exchange chromatography are also used [29]. Fibers recovered with enzymatic-gravimetric methods include cellulose, hemicelluloses, pectins, some other nonstarch polysaccharides, lignin and some resistant starch. Soluble and insoluble fibers can also be measured separately by this method [46]. However, these methods do not capture inulin and polydextrose and partially measure resistant starch. To remedy this, separate procedures have been proposed to quantify these other compounds. For instance, β-glucans can be measured by AOAC method 995.16, AAC method 32-23, and a method by McCleary and Codd [47]. Resistant starch, oligofructan, inulin, fructo-oligosaccharides, and polydextrose can also be measured independently by several methods [29].

However, these methods incompletely measure all fibers included in the Codex definition, and the use of some or all of these methods could result in underestimation of some fibers as well as overestimation of others due to double counting. The McCleary method [48] (AOAC 2009.01) was proposed to accompany the Codex definition as it allows for measurement of a complete range of dietary fiber components, including nondigestible oligosaccharides and resistant starches, in one test, without double counting or missing

Table 1: Categorization of recent definitions of fiber based on whether or not a distinction in dietary fiber source is made.

Plant source only
Food and Agriculture Organization (FAO)/World Health Organization (WHO): "Dietary fibre consists of intrinsic plant cell wall polysaccharides" [40]
Categorize fiber types based on source
Institute of Medicine (IOM): "Dietary fiber consists of nondigestible carbohydrates and lignin that are intrinsic and intact in plants Functional fiber consists of isolated, nondigestible carbohydrates that have beneficial physiological effects in humans Total fibre is the sum of dietary fibre and functional fiber" [368] *Health Canada*[1]: "Dietary fibre consists of the endogenous components of plant material in the diet which are resistant to digestion by enzymes produced by humans. They are predominantly nonstarch polysaccharides and lignin and may include, in addition, associated substances" [369] "Novel Fibre or Novel Fibre Source means a food that is manufactured to be a source of dietary fibre, and (i) that has not traditionally been used for human consumption to any significant extent, or (ii) that has been chemically processed, for example, oxidized, or physically processed, for example, very finely ground, so as to modify the properties of the fibre contained therein, or (iii) that has been highly concentrated from its plant source" [370] *Codex Alimentarius Commission*[2]: "Dietary fibre means carbohydrate polymers with ten or more monomeric units, which are not hydrolysed by the endogenous enzymes in the small intestine of humans and belong to the following categories: (i) edible carbohydrate polymers naturally occurring in the food as consumed, (ii) carbohydrate polymers which have been obtained from food raw material by physical, enzymatic, or chemical means and which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities, Synthetic carbohydrates polymers which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities" [30]
No categorization of fibers based on source
European Food Safety Authority (EFSA): "Nondigestible carbohydrates plus lignin" [371] *Food Standards Australia New Zealand (FSANZ), formerly Australia New Zealand Food Authority (ANZFA)* "Dietary fibre means the fraction of the edible part of plants or their extracts, or synthetic analogues that (a) are resistant to the digestion and absorption in the small intestine, usually with complete or partial fermentation in the large intestine; (b) promote one or more of the following beneficial physiological effects: (i) laxation, (ii) reduction in blood cholesterol, (iii) modulation of blood glucose, and includes polysaccharides, oligosaccharides (DP < 2), and lignin" [372]

[1] Health Canada is currently reviewing its definition for fiber and proposed a new definition in December 2010 which has not yet been accepted [373].
[2] Two footnotes have been included with this definition, the first indicates that substances associated with fibre (e.g., lignin, waxes, saponins, etc.) are included in this definition, unless they are isolated and reintroduced into a food. The second footnote states that the decision on whether to include carbohydrates from 3 to 9 monomeric units is up to the discretion of national authorities.

fiber compounds [48]. This method uses extended enzymatic digestion at 37°C, followed by gravimetric isolation and quantitation of high-molecular weight dietary fiber and liquid chromatography to quantitate low-molecular weight dietary fibers [49]. It is also particularly important for food labelling that fiber analysis be completed on foods as they would be eaten in order to provide more accurate fiber values that account for the effects of processing and cooking procedures [49].

For analysis of β-glucan, two AOAC methods have been adopted in oats, barley, and their products. Both methods are enzymatic colorimetric methods that use lichenase to cleave 1,3 β-bonds in β-glucan to produce oligosaccharides of various lengths that are subsequently hydrolyzed to glucose with amyloglucosidase, and then the glucose is assayed colorimetrically [39]. The AOAC method 992.28 is applicable to measure 1–12% β-glucans in oat and barley fractions, unsweetened oat cereals, and ready-to-eat cereals [50]. The AOAC method 995.16 is used to analyze β-glucan content in flours from whole grains, milling fractions, and unsweetened cereal products [47]. In addition to AOAC methods, there are other methods including enzyme-linked immunosorbent

assay (ELISA) [51], near-infrared spectroscopy [52], and fluorescence assay of complex formed between β-glucan and calcofluor [53], which are all specifically designed to measure β-glucan.

2.5. Dietary Fibers in the Prevention and Treatment of Metabolic Syndrome. Dietary fibers have been strongly implicated in the prevention and treatment of various characteristics of the metabolic syndrome. The beneficial effect of fiber-rich foods and isolated fibers, both insoluble and soluble, on obesity, cardiovascular diseases, and type 2 diabetes has been shown in randomized studies [6, 11]. Diets rich in fiber improve glycemic control in type 2 diabetes [54], reduce low-density lipoprotein (LDL) cholesterol in hypercholesterolemia [55–57], and contribute positively to long-term weight management [58]. In epidemiological studies, positive associations were noted between increased cereal consumption, a source of both insoluble and soluble fibers, and reduced risk of metabolic syndrome, cardiovascular diseases, and markers of systemic inflammation [59–61]. Diets rich in whole-grain foods have also been negatively associated with metabolic syndrome [6, 8, 11].

In comparison to insoluble fibers, soluble fibers are more potent in attenuating the presence of components of the metabolic syndrome in both animals and humans. Addition of α-cyclodextrin, a soluble dietary fiber, to high-fat-diet-fed male Wistar rats for 6 weeks attenuated weight gain and increases in plasma cholesterol and triglyceride levels while also preventing increased fecal fat content relatively to the control high fat diet [62]. Serum leptin levels were normalized and insulin sensitivity index was improved. A diet supplemented with the soluble fibers from *Plantago Ovata* husks (psyllium) and methylcellulose over 10 weeks improved obesity and lipid profile and ameliorated the unbalanced secretions of the inflammatory tumor necrosis factor-α (TNF-α) and adiponectin by the visceral adipose tissue in obese Zucker rats [63]. The diet supplemented with the soluble fermentable fiber *Plantago Ovata* husks also resulted in the greatest improvement in hyperinsulinemia and hyperleptinemia, and lowered the production and accumulation of lipids in the liver. This effect was associated with activation of the AMP-activated protein kinase (AMPK) system [63], known to increase fatty acid oxidation and decrease fatty acid synthesis [64]. In humans, a daily intake of at least 5 g of soluble fiber, particularly from whole-grain foods and fruits, reduced the presence of metabolic syndrome in patients with type 2 diabetes by 54% [65]. Moreover, a high fiber meal, in which refined-wheat flour was replaced with whole-wheat flour (16.8 g/meal), increased postprandial adiponectin concentrations in diabetic females [66]. In a cross-sectional study on diabetic men, adiponectin levels were 19% higher in the highest quintile of cereal fiber intake than in the lowest quintile [67]. High adiponectin levels are associated with improved glycemic control and insulin sensitivity, a more favorable lipid profile and reduced inflammation in diabetic females [68].

Among soluble fibers, β-glucan is the most frequently consumed and is associated with reduced presence of insulin resistance, dyslipidemia, hypertension, and obesity. The role of β-glucan in the prevention and treatment of these determinants is discussed in the following sections.

3. Beta Glucan, Obesity, and Metabolic Syndrome

Increased interest in β-glucan in the last two decades arises from its functional and bioactive properties. Of all fibers, its health benefits have been the most extensively documented, and the use of health claims with β-glucan-containing foods has been allowed in several countries including Canada, the United States of American, Sweden, Finland, and the United Kingdom [69]. Moreover, no human adverse effects have been reported following the consumption of a diet rich in β-glucan from oat or barley flour or their extracts [70].

3.1. Definition of Beta Glucan. Glucans are glucose polymers, classified according to their interchain linkage as being either α- or β-linked [71]. β-glucans are a heterogeneous group of nonstarch polysaccharides, consisting of D-glucose monomers linked by β-glycosidic bonds [72]. The macromolecular structure of β-glucan depends on both the source and method of isolation. The simplest glucan is the linear and unbranched β-(1,3)-D-glucan, found among prokaryotes and eukaryotes [73]. Another simple structural type occurs mostly in the nonlignified cell walls of cereal grains, and consist of linear β-(1,3;1,4)-D-glucans [74]. Glucans from barley, oats, or wheat are found in cell walls of the endosperm, while being concentrated in the aleurone layer of barley, oats, wheat, sorghum, and other cereals. Branched structures of β-glucans consist of β-(1,3)- or β-(1,4)-glucan backbone with either (1,2)- or (1,6)-linked β-glucopyranosyl side branches [71]. They are major structural components of the cell walls of yeast, fungi, and some bacteria [75]. The side branched β-(1,3;1,2)-D-glucan is only present in the type 37 capsule of the bacterium *Streptococcus pneumonia* [73]. Branched β-(1,4;1,6)-D-glucan and β-(1,3;1,6)-D-glucan are found in different groups of yeast, fungi, and algae [71]. In algae, β-glucans are present as storage polysaccharides or cell wall components. Some cyclic (1,2) and (1,3;1,6) β-glucans were also isolated from various bacteria. These glucans are important for plant-microbe interactions, and act as signalling molecules during plant infection [76]. Besides differences in type of linkage and branching, β-glucans can vary in terms of frequency and length of branching, degree of branching, molecular weight (from 10^2 to 10^6 daltons), polymer charge, and/or solution conformation (random coil or triple or single helix) as well as solubility [77]. All these factors play a role in shaping β-glucan-associated biological activities, and should be taken into consideration by researchers when discussing the physiological impacts of β-glucans.

The β linkages in the polymer render β-glucan nondigestible [78]. Moreover, β glucans are highly fermentable in the caecum and colon [79]. In comparison to other oat fractions, β-glucan induced the maximum growth rate and cell proliferation rate of bacteria isolated from human intestine and the maximum lactic acid productions [80].

The solubility of β-glucans is highly influenced by their structures [81]. However, no sharp distinction exists between the insoluble and soluble fractions and the ratio is highly dependent on the extraction conditions of the soluble fiber [82]. The $(1 \rightarrow 3)$-β-glucans with a high degree of polymerization (DP > 100) are completely insoluble in water [83]. This conformation allows for stronger interactions and associations between chains than between the chains and water molecules. Solubility increases as the degree of polymerization is lowered. The composition of the side substituted branches and the frequency of these branches also determine the solubility of β-glucan molecules [84]. A single $(1 \rightarrow 6)$-β linked glucose side can transform the glucan into a more soluble form in comparison to its unbranched molecule [85]. Most studies have examined the structure and properties of water-soluble β-glucans, in contrast to water-insoluble ones [86, 87].

Depending on physicochemical characteristics, various biological functions of β-glucans have been described. This review elaborates on the role of β-glucans in the prevention and treatment of the metabolic syndrome; however, a description of the immunomodulatory functions of β-glucans will be briefly examined in the following section.

3.2. Beta Glucan and Immunomodulation. Among polysaccharides that act as immunostimulants, β-glucans were found to be the most effective against infectious diseases and cancer [88]. The immunological potency of β-glucans varies with the molecular mass, solution conformation, backbone structure, degree of branching as well as the cell type that is targeted [89].

The role of 1,3 β-glucans from yeast, fungi, mushrooms, and seaweed as biological immunomodulators has been well documented in the past 40 years [90]. *In vitro*, animal and human studies have shown that 1,3 β-glucans can enhance the responsiveness and function of immune cells, stimulating both humoral and cellular immunity [91]. *In vitro* studies demonstrated that β-glucans can enhance the functional activity of macrophages and activate the antimicrobial activity of mononuclear cells and neutrophils [72, 92]. *In vivo* studies of a variety of β-glucans on the responses to pathogen infections in animals have observed increased microbial clearance and reduced mortality in lethally infected animals when exposed to β-glucans [93, 94]. Very few human studies examined the immune function of β-glucans. Three clinical studies demonstrated that pretreatment of high-risk surgical patients with intravenous yeast β-(1,3; 1,6)-D-glucan decreased the infection incidence, shortened intensive care unit length stay, and improved survival in comparison to a saline placebo injection [95–97].

3.3. Beta Glucan and Parameters of the Metabolic Syndrome. There is growing interest in the understanding of the association between β-glucans and determinants of the metabolic syndrome. Most studies have used plant β-glucans as functional viscous dietary fibers in the management of various components of the metabolic syndrome. Only two studies described a protective role of nonplant β-glucans in metabolic syndrome. In obese hypercholesterolemic men, consumption of 12 g of yeast β-(1,3;1,6)-D-glucan over 8 weeks lowered total cholesterol concentrations, and increased HDL-cholesterol levels only 4 weeks after discontinuation of glucan intake [98]. One study completed in mice found that effects of chronic consumption of chitin-glucan from a fungal source improved metabolic abnormalities induced by a high fat diet [99]. Chitin-glucan is a cell wall polysaccharide-based three-dimensional network in which the central core contains branched chitin-β-1,3 glucan. In this particular study, chitin-glucan decreased high fat diet-induced body weight gain, fat mass development, fasting hyperglycemia, glucose intolerance, hepatic triglyceride accumulation, and hypercholesterolemia, irrespective of caloric intake. These beneficial effects were mainly attributed to restoration of the composition and/or activity of gut bacteria.

The ability of plant β-glucans, which will be referred to as "β-glucans" in the following sections, to form highly viscous solutions in the human gut is thought to be the basis of its health benefits. These benefits include lowering postprandial glucose and insulin responses, decreasing cholesterol levels, and potentiating the feelings of satiety. Beta glucan has the ability to form highly viscous solutions because it is a linear, unbranched, nonstarchy polysaccharide composed of β (1–4) and β (1–3)-linked glucose molecules [100]. However, the viscosity of β-glucan depends on the molecular weight, solubility, and concentration [100–102]. For instance, high molecular weight β-glucans produce a higher viscosity than β-glucans with low molecular weights. Whether the ability to form highly viscous solutions at low concentrations provides β-glucan with unique health benefits in comparison to other soluble and fermentable dietary fibers has received little investigation. The role of β-glucan compared to other soluble fibers in affecting the components of the metabolic syndrome will be discussed in the following sections.

3.3.1. Beta Glucan and Insulin Resistance. Insulin resistance, whether or not accompanied with hyperglycemia, and type 2 diabetes are well-established components of metabolic syndrome [103].

Several soluble fibers, including β-glucan, psyllium and guar gum, reduce postprandial glucose and insulin responses, and improve insulin sensitivity both in diabetic and nondiabetic individuals [104–110]. In healthy individuals, a beverage containing 25 g/200 mL each of resistant dextrins or soluble corn fiber, a class of soluble fibers isolated from wheat or corn, attenuated postprandial glycemic, and insulinemic responses relatively to a control glucose solution (25 g glucose/200 mL of the test beverage) [111]. Arabinoxylan consumption, at 15 g/day over 6 weeks, significantly lowered the postprandial responses of serum glucose and insulin to a liquid meal challenge test in overweight subjects with impaired glucose tolerance [112]. In stroke-prone spontaneously hypertensive rats, psyllium supplementation (5%) prevented insulin resistance in response to a high-caloric diet given from 5 to 9 weeks of age [113].

Beta glucan also contributes to glycemic control. Several factors were found to influence such an interaction, including dose, food form, and molecular weight. Dose of β-glucan is important in the regulation of the effects of this

fiber on glycemic responses. Relative to other fibers, smaller amounts of β-glucan are required to bring about reductions in postprandial glucose and insulin responses in healthy subjects [114, 115], type 2 diabetic patients [116, 117] and moderately hypercholesterolemic men and women [118]. In subjects with noninsulin-dependent diabetes mellitus, consumption of three breakfasts with 4, 6, and 8.6 g of oat β-glucan in a breakfast cereal significantly decreased the peak and average increases in glucose and insulin as compared to the control [116]. A significant relationship between the amount of β-glucan in cereals and plasma glucose peak or area under the glucose curve was also observed. Similarly, a linear dose-dependent decrease in glycemic responses was noted in response to breads containing varied doses of barley β-glucan ranging from 0.1% to 6.3% [119]. Consumption of oat bran providing 7.3 g β-glucan in a breakfast cereal or 6.2 g in a bar lowered postprandial glucose responses more than an oat bran breakfast cereal providing 3.7 g β-glucan in type 2 diabetic subjects [120]. The consumption of oat bran flour containing 9.4 g of β-glucan lowered postprandial glycemia in type 2 diabetic patients in comparison to a glucose load [117]. In addition, oat bran crisps containing 3 g of β-glucan also reduced postprandial glycemia, although the reduction was only half as large as the effect induced by oat bran flour containing 9.4 g β-glucan. In hypercholesterolemic individuals, the addition of 5 g of oat β-glucan per day to a beverage consumed for 5 weeks attenuated both glucose and insulin responses compared to the control beverage [121]. However, in healthy individuals, larger doses of β-glucan are needed in order to alter their glycemic homeostasis. Unlike diabetic subjects [117], a 3 g oat β-glucan dose did not affect postprandial glycemic response in healthy subjects [122] while the intake of muesli with 4 g oat β-glucan lowered postprandial blood glucose responses in comparison to a reference meal without muesli and β-glucan in healthy individuals [122, 123].

Food form has also an influence on β-glucan's regulation of glycemia. Incorporating a high dose of oat bran β-glucan (5.2 g) into fettucini did not significantly lower postprandial blood glucose relative to the fettucini alone in healthy subjects [124]. This is perhaps because wheat pasta itself has a low glycemic response. Molecular weight is another determinant of viscosity in addition to the concentration [101], and modulates the influence of β-glucan on glycemia. A drink containing 5 g of oat β-glucan with a molecular weight 70 000 Da significantly lowered postprandial glucose and insulin levels relative to a rice drink control, while a similar drink containing barley β-glucan of molecular weight 40 000 Da had no effect [121].

Reduced insulin responses have consistently been observed following the ingestion of β-glucan [122, 125–127]. As in the case of glycemia, dose is an important factor in shaping insulin responses to β-glucan. A consistent decrease in insulin secretions was dose-dependently observed in overweight individuals in response to oat β-glucan, with significant changes reported at a dose of at least 3.8 g of β-glucan [127]. Some studies have found the impact of β-glucan on insulinemia to be independent of its glycemic effect. In healthy men, barley-enriched pasta, containing 5 g of β-glucan, induced a significant reduction in insulinemia in comparison to the control pasta without any apparent effect on glycemia [128]. Similarly, in healthy subjects, the ingestion of 50 g rye bread, containing 5.4 g of β-glucan, reduced postprandial insulinemic responses without a parallel reduction in glucose responses as compared with the control bread [109]. It was hypothesized that the low glycemic indices of pasta and rye bread may attenuate the effects of β-glucan on glucose responses.

Several mechanisms have been suggested to explain the glucose- and insulin-lowering effects of soluble fibers, more precisely β-glucan. One of the mechanisms includes the ability of soluble fibers to form viscous solutions. Delayed gastric emptying occurs with increased digesta viscosity [129–131], slowing subsequent digestion and absorption [132]. High digesta viscosity decreases enzyme diffusion [133] and stimulates the formation of the unstirred water layer [134], decreasing glucose transport to enterocytes [31]. Reducing the viscosity of guar gum following acid hydrolysis resulted in concurrent loss of its clinical efficacy [31]. A relationship was noted between guar gum viscosity and its glycemic response. Moreover, it was stated that the viscosity of β-glucan could account for 79–96% of the changes in glucose and insulin responses to 50 g glucose in a drink model [135].

Evidence for delayed stomach emptying following the consumption of β-glucan emerged from human and animal studies. The quantity of exogenous glucose appearing in plasma was 18% lower, during the first 120 min, following the polenta meal with 5 g oat β-glucan in comparison to the control polenta meal in overweight individuals [136]. Similarly, the addition of ^{13}C-labelled glucose to a meal containing 8.9 g β-glucan, consumed over 3 days, lowered the appearance of exogenous ^{13}C-glucose in plasma by 21% relatively to a control meal without β-glucan [137].

Short-chain fatty acids resulting from the anaerobic bacterial fermentation of soluble dietary fibers such as β-glucan in the colon [138] offer another explanatory mechanism for the protective effects of soluble fibers on glucose and insulin homeostasis. The short-chain fatty acids propionic and butyric acid increased muscle expression of the insulin-responsive glucose transporter type 4 (GLUT-4) via the peroxisome proliferator-activated receptor (PPAR) γ [113]. The activation of PPARγ also increased GLUT-4 content in adipocytes [139]. Stroke-prone spontaneously hypertensive rats consuming psyllium supplementation, at 5% in a high caloric diet, witnessed improved muscle insulin sensitivity via short-chain fatty acid-induced increased membrane GLUT-4 expression in comparison to cellulose supplementation [113].

In conclusion, due to its viscosity and fermentability, β-glucan plays a significant protective role against insulin resistance in various populations.

3.3.2. Beta Glucan and Dyslipidemia. Individuals with metabolic syndrome often present with atherogenic dyslipidemia, characterized by elevated concentrations of triacylglycerols and low levels of HDL cholesterol in blood [3]. This lipid profile presents an individual with a high risk for cardiovascular disease.

Soluble fibers have the most reported beneficial effects on cholesterol metabolism. In a meta-analysis, soluble fibers pectin, psyllium, oat bran, and guar gum were all proven to be equally effective in reducing plasma total and LDL cholesterol levels [55]. When included within a low saturated fat and cholesterol diet, soluble fibers lowered LDL cholesterol concentrations by 5–10% in hypercholesterolemic and diabetic patients [55, 108]. The consumption of 14 g per day of *Plantago Ovata* husk for 8 weeks induced a significant reduction in total cholesterol, LDL cholesterol, and oxidized LDL in mild-moderate hypercholesterolemic patients [140]. Conversely, soluble fibers from barley, oats, psyllium, and pectin had no effect on HDL cholesterol levels [55, 141].

Variable effects of soluble fibers on triglyceridemia have been noted. In two meta-analyses, soluble fibers, including barley, oats, psyllium, and pectin, had no significant impacts on triglyceride concentrations [141]. Other studies have described hypotriglyceridemic effects of soluble fibers in various populations. In a study on type 2 diabetic patients, the intake of a high-soluble fiber diet (25 g/day) over a period of 6 weeks lowered triglyceride concentrations by 10.2% [142]. The soluble fiber in *Plantago Ovata* husk reduced triglyceridemia in human secondary cardiovascular disease risk trials, when consumed at 10.5 g/day over 8 weeks [143]. Similarly, the consumption of arabinoxylan at 15 g/day over 6 weeks significantly reduced postprandial triglyceride responses in overweight subjects with impaired glucose tolerance [112]. Discrepancies in findings could be attributed to the variability in fiber structure, the degree of solubility and viscosity, different administered doses, the duration of administration, and baseline triglyceride levels of the subjects.

The effect of β-glucan on lipid parameters has been intensively investigated; however, differing results have been found. These inconsistencies in findings may be explained by several factors including the sources, dose and molecular size of β-glucans, dietary composition, food preparation, food state (solid versus liquid), subject's baseline cholesterol concentrations, and study design [144] as well as the cultivar of barley and oat being used and their growing conditions [145, 146]. Although varied effects of barley and oat-derived β-glucans have been reported on lipid homeostasis, they were not established as significant differences since β-glucan content of these two cereals is almost comparable [147, 148]. In the following sections, the impacts of barley and oat β-glucans on lipid parameters will be separately discussed.

A limited effect of barley β-glucan on lipid parameters has been described and the dose of barley β-glucan appears to be a major determinant of this effect. In a meta-analysis of randomized clinical trials, the consumption of 3 to 10 g of barley β-glucan per day, over 4 to 6 weeks, significantly lowered total and LDL cholesterol in subjects with different dietary backgrounds [141]. In another meta-analysis of 8 randomized controlled trials, participants receiving 3 to 10 g of barley β-glucan per day, over a duration ranging between 4 and 12 weeks, had significant reductions in total cholesterol, LDL cholesterol, and triglycerides in comparison to control group participants, irrespective of whether a low-fat or a Step I diet was given [144]. Moreover, the consumption of pearl barley, providing 7 g of β-glucan per day over 12 weeks, significantly reduced serum concentrations of total cholesterol and LDL cholesterol in hypercholesterolemic Japanese men [149]. Both total and LDL cholesterol concentrations were significantly reduced following the consumption of the high barley β-glucan diet (6 g/day), in comparison with the diet low in barley β-glucan (0–0.4 g/day) in hypercholesterolemic subjects [150, 151]. In contrast, daily ingestion of 10 g of barley β-glucan over 4 weeks in the form of bread, cakes, muffins or savory dishes, had no effect on serum lipoprotein profile in hypercholesterolemic men in comparison with the control group [152]. In addition, neither 5 g nor 10 g of barley β-glucan consumed daily in a beverage over 5 weeks had a significant impact on serum lipids in hypercholesterolemic subjects as compared with control [121]. Thus, in addition to dose, the food vehicle delivering barley β-glucan also affects its regulation of lipid responses.

Despite conflicting results, oat β-glucans were found to be strongly effective in modulating plasma lipid parameters. As in the case of barley β-glucan, the ingested dose of oat β-glucan appears as a limiting factor. The US Food and Drug Administration and Health Canada have accepted 3 g as an effective daily intake of oat β-glucan to reduce serum LDL cholesterol [74, 153]. In a meta-analysis on oats containing 2 to 10 g per day of β-glucan, a net change of -3.1 mg/dL to -15.5 mg/dL for total cholesterol and of -2.9 mg/dL to -14.3 mg/dL for LDL cholesterol was observed [55]. A significantly greater serum cholesterol reduction was reported after the intake of 4 g of β-glucan as compared to 2 g from oat bran or oat meal incorporated into muffins, cereals, and shakes [154]. Increasing the dose to 6 g of β-glucan did not provide any further reduction in serum cholesterol concentrations. Similarly, a beverage providing 5 g of β-glucan per day from oats significantly lowered total and LDL cholesterol over a period of 5 weeks compared to a control beverage, in hypercholesterolemic individuals [121]. No additional benefit was reported on serum lipids when increasing the daily dose of oat β-glucan to 10 g. A bread containing 6 g of oat-derived β-glucan significantly improved HDL cholesterol and diminished LDL cholesterol, non-HDL cholesterol, total cholesterol/HDL cholesterol ratio, and LDL cholesterol/HDL cholesterol ratio, over 8 weeks compared to whole-wheat bread, in overweight individuals with mild hypercholesterolemia [155]. Similarly, the consumption of 6 g/day of concentrated oat β-glucan in the form of powder for 6 weeks significantly reduced both total and LDL cholesterol in hypercholesterolemic adults, with the reduction in LDL cholesterol being greater than that in the control group [156]. A once-daily consumption of 4 g of β-glucans from oats, incorporated into a ready-meal soup, reduced LDL cholesterol levels by 3.7% over 5 weeks in a group of hyperlipidemic healthy subjects as compared with a control diet [157]. In contrast, in some studies, the reductions were small and nonsignificant, around less than 5% for LDL cholesterol, in comparison to control groups [158–162]. Food vehicle, rather than dose, seems to explain such minimal lipid responses to oat β-glucan ingestion in these studies. A once-daily consumption of 20 g of an oat bran concentrate (containing 3 g of oat β-glucan) in the form

of cereal for 12 weeks did not affect total cholesterol and LDL cholesterol as compared to 20 g wheat bran (control) [161], nor did 4 weeks of 5.9 g of oat bran β-glucan administered daily in bread and cookies [162].

The mode of administration of β-glucan is another determinant to consider when explaining such variability in results since structural changes in β-glucan may result from food processing or storage of barley and oat products. The consumption of oat β-glucan in a variety of foods, such as muffins and cereals, effectively lowered LDL cholesterol [163], suggesting that the structure and molecular weight of oat β-glucan are maintained in these products. On the other hand, the effects of oat β-glucan administered in bread are controversial. The consumption of bread providing 140 g of rolled oats per day led to an 11% reduction in serum total cholesterol concentrations [164]. However, other studies found no hypocholesterolemic effect of incorporating oats into bread [158, 165–167]. Bread making can cause significant depolymerization of β-glucan, primarily induced by β-glucanase enzymes present in wheat flour [162, 168]. The activation of these enzymes depends on the processing technique used in bread making.

The varied responses of cholesterol-rich lipoproteins to β-glucans could be also attributed to differences in molecular weight and solubility of the fibers. Molecular weight, solubility, and viscosity are important physicochemical properties of β-glucan, which are strongly affected by the genetic attributes of oat and barley grains [169]. For instance, oat β-glucans have a higher molecular weight than barley β-glucans [102, 170–172]. Only 15–20% of barley β-glucans are water soluble while almost 70% of the oat β-glucans are soluble in water [173]. Relatively to barley β-glucan, the higher molecular weight of oat β-glucan is attributed to a greater content and frequency of side branches rather than to a higher degree of polymerization, explaining its higher degree of water solubility [83, 85]. As viscosity is highly influenced by the molecular weight and solubility of β-glucan, a lower molecular weight and/or solubility of β-glucan are expected to reduce its resultant viscosity and consequently its cholesterol-lowering effects. Highly water-soluble β-glucan, with moderate to high molecular weight, reduced serum LDL cholesterol better than β-glucan with low water-solubility and low molecular weight [174]. This explains the lower reported effects of barley β-glucan on lipid parameters as compared to oat β-glucan.

The hypocholesterolemic properties of β-glucans are explained by various mechanisms some of which are shared with other soluble dietary fibers. Altering bile acid excretion and the composition of bile acid pool is one of the mechanisms. Dietary fibers are associated with increased bile acid excretion and increased activity of cholesterol 7α-hydrolase, a major enzyme leading to cholesterol elimination in the body [175]. Beta glucans can decrease the reabsorption of bile acids and increase their transport towards the large intestine [176], promoting their increased microbial conversion to metabolites and their higher excretion, subsequently inducing increased hepatic synthesis of bile acids from circulating cholesterol [177]. This mechanism is strongly related to β-glucan-induced increased viscosity in the small intestine [128, 178, 179] and consequently slowed gastric emptying, digestion, and absorption [179]. In addition, some soluble fibers decrease the absorption of dietary cholesterol by altering the composition of the bile acid pool. In fact, oat bran increased the portion of total bile acid pool that was deoxycholic acid [180], a microbial byproduct of bile acid which decreases the absorption of exogenous cholesterol in humans [181].

The fermentation of some soluble fibers, including β-glucan, provides another explanation for their cholesterol-lowering effects. Fermentation changes the concentration of bile acids in the intestinal tract of rats [177] as well as the production of short-chain fatty acids, which influence lipid metabolism. For example, propionate is thought to suppress cholesterol synthesis, though results are still inconclusive [182–186] and acetate may contribute to the lowering of cholesterol circulating levels [187]. It should be well noted that differences between soluble fibers in the relative production of acetate, propionate, butyrate, and total short-chain fatty acids do exist. Oat β-glucan ferments more rapidly than guar gum, reflected in higher concentrations of total short-chain fatty acids, in general, and of acetate and butyrate, in particular [32]. However, such differences may not be that important to generate varied degrees of hypocholesterolemic impacts among soluble fibers.

Few mechanisms, most not clearly elucidated, have been suggested in order to explain the hypotriglyceridemic properties of soluble fibers, including β-glucan. Two mechanisms include a possible delay in the absorption of triglycerides in the small intestine [188], as well as a reduced rate of glucose absorption [189]. Glucose-induced hypertriglyceridemia, via the process of *de novo* lipogenesis, is well established in the literature [190]. Furthermore, direct inhibition of lipogenesis by soluble fibers is also suggested as an explanatory mechanism. The hypotriglyceridemic effect of oligofructose was reported to result from the inhibition of hepatic lipogenesis via the modulation of fatty acid synthase activity [191, 192]. In an *in vitro* study, β-glucan extracts from oat and barley flour inhibited the *in vitro* intestinal uptake of long-chain fatty acids and cholesterol and downregulated various genes involved in lipogenesis and lipid transport in rats [147].

In conclusion, β-glucan possesses similar hypocholesterolemic properties as other soluble dietary fibers. However, the hypotriglyceridemic impacts of β-glucan have not been fully determined and warrant further investigation. Additionally, further studies need to be conducted in order to optimize β-glucan's hypolipidemic dose and to investigate the long-term effect of β-glucan supplementation on blood lipid chemistry. The eventual goal would be to combine β-glucan supplementation with other dietary means of controlling blood lipids, and to consequently prevent the need for cholesterol-lowering drugs in hyperlipidemic patients.

3.3.3. Beta Glucan and Blood Pressure. Hypertension is another core component of the metabolic syndrome, and is an established risk factor for heart diseases, stroke, and renal diseases [193].

The effects of soluble dietary fibers, including β-glucan, on arterial blood pressure have been the least studied among

the components of the metabolic syndrome. In one meta-analysis, increased dietary fiber consumption provided a safe and acceptable means to reduce blood pressure in patients with hypertension [194]. In a randomized crossover study on hyperlipidemic adults, small reductions in blood pressure were reported following the intake of a high-fiber diet containing β-glucan or psyllium (8 g/day more than the unsupplemented food in the control diet) over 4 weeks [195]. In another randomized parallel-group study on hypertensive and hyperinsulinemic men and women, the oat cereal group (standardized to 5.52 g/day of β-glucan) experienced a significant reduction in systolic and diastolic blood pressure in comparison to the low-fiber cereal control group (<1 g/day of total fiber) over 6 weeks [196]. Similarly, in a randomized double-blind placebo-controlled trial on participants with untreated elevated blood pressure or stage 1 hypertension, the consumption of 8 g/day of supplemented soluble fiber from oat bran over 12 weeks significantly reduced both systolic and diastolic blood pressure in comparison to the control [197].

Various mechanisms underlying the antihypertensive effects of soluble dietary fibers have been hypothesized. Insulin resistance is a major underlying mechanism contributing to the development of hypertension [198] and soluble fibers may affect blood pressure by modulating insulin metabolism [199]. Reductions in plasma cholesterol, observed following the ingestion of soluble fibers, are also associated with improvements in endothelium-mediated vasodilation [200, 201]. Preliminary findings in animals support a direct relationship between changes in circulating cholesterol levels and blood pressure [202]. Finally, soluble fiber-induced weight loss, which will be discussed in the coming section, has also been suggested as a potential mechanism. Increased body weight is a strong risk factor for hypertension [203].

In conclusion, additional studies are still needed in order to fully elucidate the mechanisms underlying the protective effects of soluble fibers against hypertension. Moreover, the association between β-glucan and blood pressure remains to be further explored.

3.3.4. Beta Glucan, Satiety, and Obesity. Central obesity is a well-established component of the metabolic syndrome [3]. One potential countermeasure to the current obesity epidemic is to identify and recommend foods that spontaneously reduce energy intake by inducing satiation and increasing satiety.

Dietary fiber has documented effects on satiety, food intake, and body weight although the outcomes have not been consistent [204]. A number of randomized controlled trials have shown weight reduction with diets rich in dietary fiber or dietary fiber supplements [205–208], while others have not [209]. However, a meta-analysis of 22 clinical trials concluded that a 12 g increase in daily fiber intake is associated with a 10% reduction in energy intake and a 1.9 kg reduction in weight during an average study duration of 3.8 months [204]. More specifically, the soluble dietary fiber glucomannan, which has a strong water-holding capacity, resulted in a significantly greater reduction of weight, when consumed at a dose of 1.24 g daily for 5 weeks in conjunction with an energy-restricted diet, as compared to the placebo energy-restricted group [210].

Despite the clear association between soluble fibers and weight loss, their effects on subjective measures of satiety are not conclusive. However, soluble fibers with viscosity-producing properties, including guar gum, pectin, psyllium, and β-glucan, are more strongly associated with reduced hunger and/or appetite perceptions than low/no fiber condition [211]. For example, the addition of 2.5 g of guar gum to a semisolid meal prevented an increase in appetite, hunger, and desire to eat in overweight male volunteers [212]. The soluble resistant dextrins promoted, in a dose-dependent manner, increased satiety when added to desserts and to carbohydrate-based meals [213–215]. Moreover, a nutrition bar containing guar gum (5.7 g guar gum and 9.1 g other fibers) increased perceived fullness and decreased hunger sensations as compared to a reference bar (6.4 g dietary fiber) [216].

Barley, a source of β-glucan, possesses satiating properties when fed intact. Subjects described to be significantly less hungry before lunch after consuming barley—but not wheat—and rice-containing foods [217]. Barley-based foods enhanced as well satiety when compared to a high-glycemic index food or a food with no dietary fiber [218–220]. This effect does not appear specific to one type of barley, as different cultivars of barley produced an equivalently greater satiety feeling, up to 180 min postprandially, in comparison to white wheat bread [218].

In contrast to whole barley, both positive [128, 221–223] and negative [220, 224–226] effects of β-glucan on satiety have been described. A beverage containing oat β-glucan, at levels of 10.5 g/400 g portion and 2.5 g and 5 g/300 g portion, increased fullness sensation in comparison to the beverage free of fiber in healthy volunteers [222, 227]. Similarly, a preload of 5.2% barley β-glucan-enriched biscuits significantly suppressed appetite ratings in healthy adolescents, without modifying subsequent food intake at lunch, as compared with control biscuits [228]. In healthy participants, a 3% barley β-glucan-enriched bread induced a higher reduction of hunger and increase in fullness and satiety as compared to the control bread. This was also associated with a significant reduction of energy intake at the subsequent lunch [223]. In contrast, a meal replacement bar containing 1.2 g of barley β-glucan (from 8.0 g barley), consumed at breakfast on 2 consecutive days by healthy subjects, did not modify appetite scores or energy intake at subsequent lunch in comparison to a control bar containing only 0.3 g β-glucan (from 6.8 g oats) [226]. Moreover, muesli containing 4 g of oat β-glucan did not induce differential satiating effects than an isocaloric portion of cornflakes in healthy individuals [123], as a dose of 2 g of β-glucan in cereal test meals did not affect satiety ratings in comparison to isocaloric glucose load in overweight participants [225].

The efficacy of β-glucan on satiety depends on several factors. Dose is one of the major determinants. A beverage (300 g) containing 5 g of oat dietary fiber (2.5 g of β-glucan) produced significantly higher ratings of satiety than the

fiber-free beverage [227]. However, when the dose was raised to 10 g of oat fiber (5 g of β-glucan), no additional impact on satiety scores was reported [227]. The physical effects of β-glucans on the ingesta appear to be fundamentally important in shaping their satiating properties. This effect is largely determined by molecular size and solubility of β-glucans [229]. The molecular weight of β-glucan, a major determinant of solubility, varies from 31 to 3100 kilodaltons [230] and can change during isolation, purification, and extraction procedures [231]. Such variability in the molecular weight and solubility of β-glucan may explain its varied impacts on satiety. Finally, the carrier food also plays a role in defining the interaction of β-glucans with satiety. Almost all studies that did not report any significant influence of β-glucan on satiety used solid or semisolid foods as carrier foods, unlike studies that incorporated β-glucan into liquid meals [227]. Solid foods are known to increase satiety and decrease hunger more effectively than liquid ones [232]. Thus, the larger satiating effect of solid food per se may mask the satiating potential of β-glucans.

Since almost all studies did not account for these factors and were run under different experimental conditions (different β-glucan dose, various molecular weights and food sources of the fiber, different dosing protocols, and diverse types of subjects), ranking the satiating power of β-glucan is still not possible at this stage. Moreover, another concern to be addressed in future studies is the type of control to use. No dietary fiber that may function as a control for satiety studies has been actually identified. In almost all studies, the control food was the same food with either a lower amount or a complete absence of β-glucans.

As the effect of β-glucan on satiety is still unclear, its effect on body weight regulation is less clear. In a study on diabetic patients, the supplementation of β-glucan from oats, at a dose of 9 g/day over 24 weeks, did not have any significant effect on body weight [69, 233]. In another study on hyperlipidemic patients, weight differences were not observed following the consumption of a diet rich in oat β-glucan (8 g/day), over 1 month, as compared to the control group [195]. It should be noted that the body weight was not the primary concern of these studies as they focused on changes in blood sugar or blood lipids. Even at moderate (5-6 g/d) and high (8-9 g/d) doses, the addition of oat β-glucan to an energy-restricted diet did not enhance the effect of energy restriction on weight loss in overweight women after a period of 3 months [234]. In contrast, hypercholesterolemic Japanese men consuming a mixture of rice and pearl barley with a high β-glucan content (7 g/day), for 12 weeks, experienced a significant reduction in body mass index, waist circumference, and visceral fat in comparison to the placebo group consuming rice alone [149]. Variations in the food sources of β-glucan, rather than in the dose and the duration of administration, may explain such contradictions in findings and appear as critical determinants of body weight regulation.

The satiating properties of soluble dietary fibers have been explained by various mechanisms, all of which are related to several stages in the process of appetite regulation such as taste, gastric emptying, absorption, and fermentation [235]. Firstly, the viscosity of soluble fibers plays an important role in their ability to induce satiety [222, 236, 237]. The most viscous β-glucan-enriched beverage increased perceived satiety significantly more than the beverage containing the same amount of fiber but with enzymatically lowered viscosity [227]. A higher viscosity meal delays gastric emptying [130, 131, 238] and slows the digestion and absorption of nutrients, more precisely glucose, due to reduced enzymatic activity and mucosal absorption [31, 239], leading to early satiety sensations. The overall gastric emptying rate of healthy volunteers, as assessed by the paracetamol absorption test, was slower after the high viscosity oat bran-enriched beverage as compared to the low viscosity drink [240]. Secondly, the lower palatability of fiber-rich meals may affect food intake in a negative manner [241–243]. A strong inverse relationship is described between palatability and satiation [244]. When chronically consumed, products enriched with β-glucan had lower sensory acceptance [121, 245]. Third, the reduced glycemic and insulinemic responses to soluble fibers, including β-glucan, can be also responsible for their satiating properties. A significant inverse relationship is reported between satiety and glucose and insulin responses to carbohydrate-rich breakfast cereals [246, 247] and to beverages with different glycemic effects [248]. However, other studies did not report any association of glucose and insulin postprandial levels with satiety [249, 250]. They suggested that the release of putative satiety peptides is a more crucial component of mechanisms initiating and maintaining satiety. Such statement leads to the fourth suggested mechanism that delineates the role of short-chain fatty acids in appetite control. Short-chain fatty acids regulate the release of various gut hormones, which play an important role in satiety signaling. Most β-glucan consumed is fermented in the caecum and colon, producing short-chain fatty acids [79]. The role of short-chain fatty acids in appetite regulation and the potential underlying mechanisms will be elucidated in the following sections.

(i) Short-Chain Fatty Acids and Appetite Regulation. Dietary fibers pass as unaffected through the small intestine, and upon reaching the colon, anaerobic bacteria degrade some dietary fibers via a fermentation process, yielding short-chain fatty acids. The fermentability of soluble fibers by colonic microbiota is greater than that of insoluble fibers. Pectin, resistant starches, gums, and polyfructans (such as inulin) are the most highly fermented substrates. Around 80% of short-chain fatty acids present in the human colonic lumen are in the form of acetate, propionate, and butyrate [251]. About 90% of these short-chain fatty acids are rapidly absorbed in the colon; butyrate is almost entirely used by the colonocytes as their preferred energy substrates [252] while propionate is primarily removed by the liver [251]. On the other hand, acetate passes more freely into the peripheral circulation [253]. Several functions are attributed to short-chain fatty acids, being recently proposed as key energy homeostasis signaling molecules [254].

Accumulating evidence has attributed the satiating effects of fermentable carbohydrates to short-chain fatty acids, their

major fermentation products [255]. Short-chain fatty acids regulate appetite through several mechanisms. First, short-chain fatty acids have a role in slowing gastrointestinal motility, thus controlling digestion and nutrient absorption and eliciting an anorexigenic effect. The majority of the studies linking short-chain fatty acids to gastrointestinal motility stems from ruminant animal studies [256], where the production of short-chain fatty acids is greater than that in humans due to differences in gut physiology [257]. However, there are some studies on nonruminants showing that short-chain fatty acids may regulate the overall transit time of the digesta through the large intestine [258, 259]. Such responses were hypothesized to occur via three possible pathways: (1) short-chain fatty acid stimulation of the vagal nerves in the gut, (2) a direct effect of short-chain fatty acids on intestinal smooth muscle tone, and (3) as a consequence of the indirect changes in the secretion of peptide YY (PYY) and other regulatory peptides known to play a role in gastrointestinal motility [260]. In addition, short-chain fatty acids were suggested to regulate gastrointestinal motility by affecting the release of the gastrointestinal 5-hydroxytryptamine (5-HT) via the activation of the free fatty acid receptor 2 (FFA2), the major receptor for short-chain fatty acids. 5-HT or serotonin is a neurotransmitter in the central nervous system, known to modulate mood, behavior, and appetite [261]. Though the central actions of 5-HT are the most documented, 95% of endogenous 5-HT is found peripherally in the gastrointestinal tract [262]. The activation of various 5-HT receptor subtypes stimulates vagal nodose neurons and consequently prolongs colonic transit time [263, 264]. Short-chain fatty acids also regulate appetite by modulating the release of various appetite-related hormones throughout the gastrointestinal tract [265]. The effects of short-chain fatty acids on the release of some of these gut hormones, including PYY, glucagon-like peptide 1 (GLP-1), cholecystokinin (CCK), and ghrelin, will be discussed in the following sections, providing partial explanations for the reported impacts of soluble dietary fibers in general, and of β-glucan specifically, on satiety hormones and consequently on appetite and food intake.

Peptide YY. Peptide YY is a 36-amino acid peptide, first isolated from porcine upper small intestine [266]. Two circulating forms of PYY are released by L cells in the distal gut, $PYY_{1–36}$ and $PYY_{3–36}$, which is the truncated major circulating form [267]. PYY is secreted throughout the entire length of the gastrointestinal tract, with the highest concentrations found in the colon and rectum [268]. Circulating PYY levels are the lowest in the fasting state and increase following the consumption of a meal, peaking at 1-2 hours and remaining elevated for several hours. Peripheral PYY administration decreased food intake and body weight gain in rats [269]. Similarly, it decreased appetite and food intake both in lean and obese humans [269, 270].

An increased PYY response was consistently described following the consumption of various soluble dietary fibers. Postprandial PYY clearly increased after the consumption of psyllium-enriched test meals in healthy volunteers [271]. The consumption of PolyGlycopleX, a novel functional fiber complex manufactured from three dietary fibers to form a highly viscous polysaccharide with high water-holding and gel-forming properties, for 3 weeks resulted in significantly increased fasting PYY levels as compared to the control product in healthy adults [272]. Moreover, a meal tolerance test in overweight and obese adults consuming 21 g of oligofructose for 3 months resulted in a greater increase in PYY concentrations as compared to the placebo group, concomitant with a reduced self-reported caloric intake [273].

The ability of β-glucan to increase PYY release was reported in various population groups. In healthy subjects, bread enriched with 3 g barley β-glucans induced a 16% higher overall PYY response in comparison to the control bread [223]. Even in overweight men and women, PYY levels responded positively and in a dose-responsive manner to increasing oat β-glucan concentrations, ranging from 2.16 g to 5.45 g per serving, in the first 4 hours after a meal [274].

The fermentation process of β-glucan and the subsequent generation of short-chain fatty acids provide a major explanatory mechanism for β-glucan-induced PYY release. The direct infusion of short-chain fatty acids into rabbit and rat colons significantly increased PYY secretions [275, 276]. The stimulatory effects of short-chain fatty acids on PYY secretions are mainly attributed to a direct interaction between short-chain fatty acids and PYY cells. In fact, FFA2 (also known as GPR43), the major receptor for short-chain fatty acids, is colocalized with PYY immunoreactive enteroendocrine L cells both in rat ileum and human colon [259, 277].

Glucagon-Like Peptide 1. Glucagon-like peptide 1 is cosecreted with PYY from the intestinal L cells, encoded by the proglucagon gene [278]. It is described with a potent incretin effect, stimulating insulin secretion in a glucose-dependent manner. Circulating GLP-1 levels rise following nutrient ingestion, in proportion to the energetic content of the meal [279]. An acute intracerebroventricular administration of GLP-1 to rodents induced a decline in short-term energy intake [280], and was associated with a reduced body weight following repeated administration [281]. Similarly, an intravenous infusion of GLP-1 both in normal weight and in obese subjects resulted in a dose-dependent reduction in food intake [282].

The effects of β-glucan on GLP-1 release have not been yet elucidated; however, the effects of other soluble fibers have been investigated. Variable GLP-1 responses to soluble dietary fiber intake were described, whether elevated, inhibited, or unaffected. The exposure to a diet supplemented with 10% oligofructose for 4 weeks increased the number of GLP-1-producing L-cells as well as endogenous GLP-1 production in the proximal colon of male Wistar rats in comparison to a standard diet [283]. In humans, a standard breakfast containing galactose (50 g) and guar gum (2.5 g) increased, extendedly, GLP-1 release in healthy women as compared with a standard control breakfast [284]. In contrast, in normal-weight males, resistant (pregelatinized) starch (50 g) produced a smaller GLP-1 response than digestible starch (50 g) [285]. On the other hand, the ingestion of pasta

enriched with a small amount of psyllium fiber (1.7 g) did not modify postprandial GLP-1 responses in comparison to the control pasta in healthy subjects [286]. Such discrepancies in findings could be attributed to differences in the structures and food sources of ingested soluble fibers and their administered doses.

Colonic fermentation appears to be essential in explaining GLP-1 release in response to soluble dietary fibers, despite inconsistent findings. Though supplementation with fermentable carbohydrates has been consistently associated with increased colonic proglucagon mRNA expression [287–293], only few studies detected increased plasma GLP-1 circulating levels in parallel [288–290, 293–295]. Rats fed high doses of the fermentable inulin-type fructans (100 g/day), over 3 weeks, had higher mRNA expressions in the proximal colon and plasma concentrations of GLP-1 as compared to those fed a standard diet [288]. The exposure of male Wistar rats to a diet supplemented with 10% of inulin-type fructans, for 3 weeks, resulted in a higher caecal pool of GLP-1, an increase in GLP-1 and of its precursor proglucagon mRNA concentrations in the proximal colon, and an increase in the circulating levels of GLP-1 as compared to the standard diet [289]. In normal-weight adults, the microbial fermentation of 16 g of soluble fructan per day, over 2 weeks, induced increased levels of GLP-1 in circulation as compared to the control dextrin maltose [296]. A strong association between postprandial hydrogen production and plasma GLP-1 concentrations was also reported. On the contrary, others have shown no effect of fermentable carbohydrates on circulating GLP-1 levels, whether acutely [297] or over a short duration of 6 days [298]. Based on these findings, the duration of supplementation is an important factor to consider when suggesting fermentation as a basis for soluble fibers-induced GLP-1 release. A sufficient time of 2-3 weeks must be given in order to allow adaptation of the gut microbiota to the additional fermentable carbohydrate within the diet for maximal fermentation to take place [299] and for GLP-1 levels in circulation to be subsequently affected.

Cholecystokinin. Cholecystokinin was among the first hormones shown to modulate food intake [300]. It is secreted from the I cells of the small intestine in response to food ingestion [301]. Cholecystokinin circulating levels rise rapidly after a meal, reaching a peak within 15 minutes. It was found to reduce food intake when infused both in rodents and humans [301, 302]. In fact, plasma CCK levels are strongly associated with subjective measurements of satiety in women [303].

Limited studies described the interaction between soluble dietary fibers and CCK release. Various soluble fibers, including hydrolyzed guar gum (20 g) in obese females [304], β-glucan in barley pasta (15.7 g) in healthy men [128], and isolated fibers from oatmeal and oat bran (8.6 g) in healthy men [305], produced greater and longer-lasting postprandial CCK levels in comparison to low-fiber or placebo meals. A study on overweight women revealed a dose-dependent effect of increased oat β-glucan concentrations, ranging from 2.16 to 5.68 g per serving, on CCK levels in the first 4 hours after a meal, with a significant CCK release observed at a minimum dose of 3.8 g of β-glucan [127].

The role of fermentation and more specifically short-chain fatty acids in regulating CCK release is still poorly understood. In pigs, ileal infusion of short-chain fatty acids did not affect CCK circulating levels [306]. Thus, the fermentation process per se does not explain CCK responses to β-glucan ingestion. Additional mechanisms underlying the stimulatory effects of β-glucan on CCK secretions remain to be explored.

Ghrelin. Ghrelin is the only known orexigenic hormone in the gut. It was initially identified as an endogenous ligand for growth hormone secretagogue receptor (GH-SR) in rat stomach [307]. Circulating ghrelin levels increase before meals and fall rapidly after eating [308]. Both central and peripheral administration of ghrelin increased food intake and body weight in rodents [309, 310].

The effects of soluble fibers, including β-glucan, on postprandial ghrelin are not fully understood. The consumption of a small amount (4 g) of noncaloric soluble psyllium fiber with water suppressed postprandial ghrelin levels as effectively as a 585-Kcal mixed meal in healthy women [311]. On the other hand, postprandial plasma ghrelin did not decrease following gastric distention with a noncaloric liquid meal containing 21 g of soluble guar gum fiber in comparison to carbohydrate-, protein-, and fat-rich meals [312]. Moreover, a 300-Kcal meal enriched with 23 g of psyllium fiber inhibited postprandial suppression of plasma ghrelin levels [313]. When compared to a control breakfast, a soluble arabinoxylan fiber-enriched breakfast (6 g) induced a shorter postprandial ghrelin decline [314] whereas bread enriched with 3 g barley β-glucans resulted in 23% lower ghrelin responses than a control bread [223]. Discrepancies in findings could be explained by variations in the physical and chemical properties of ingested soluble fibers, their different administered doses, and the forms of ghrelin being measured in circulation.

Several mechanisms were suggested to explain fiber-induced ghrelin suppression, most importantly fermentation. Feeding a diet supplemented with 10% of the fermentable inulin to rats over 3 weeks significantly reduced ghrelin levels in comparison to a standard diet [289]. The ingestion of 56 g of high-fructose corn syrup (HFCS) plus 24 g inulin induced greater postprandial ghrelin suppression as compared to HFCS without inulin, both at 4.5 and 6 hours, in healthy subjects [315]. Such colonic fermentation may reduce ghrelin via increasing circulating PYY levels. Administration of PYY to humans reduced serum ghrelin levels [316]. In addition to colonic fermentation, other mechanisms were also hypothesized. A possible inner-gastric pathway may operate through gastric somatostatin, which is released following the consumption of beet fiber in diabetic individuals [317]. Somatostatin administration decreased ghrelin secretion in rats [318] and lowered circulating ghrelin levels in humans [319]. In addition, GLP-1 release in response to soluble fibers is another potential mechanism. Infusion of GLP-1 into isolated rat stomach suppressed ghrelin secretions [320].

In conclusion, there is evidence for the satiety efficacy of β-glucan. Such satiating capacity appears to be comparable to that of other soluble viscous and fermentable fibers. Although several mechanisms may explain the satiating properties of β-glucan, the generation of short-chain fatty acids through colonic fermentation has the most documented effects. Short-chain fatty acids affect satiety by primarily modulating the release of various appetite-regulating hormones, including PYY, GLP-1, and ghrelin. However, other yet unknown mechanisms, independent of short-chain fatty acids, may be involved in the regulation of gut hormones by β-glucans. Since research in this area is still limited, such mechanisms necessitate further investigation. Combining knowledge from previous studies, a minimum level of β-glucan, ranging from 4 to 6 g, appears to be essential for its gastrointestinal appetite-regulating effects [321]. However, additional studies addressing the role of dose, form, molecular weight and carrier food on the interaction between β-glucan and satiety are still needed before drawing solid conclusions. Moreover, the role of β-glucan in long-term weight regulation is still not well understood and needs to be further explored. Inconsistencies in data regarding the effect of dietary or supplementary β-glucan on body weight highlight the need for additional research.

4. Beta Glucan-Fortified Foods in the Market

4.1. Global Dietary Fiber Intake. Insufficient intake of dietary fiber has been reported worldwide. However, the estimates of fiber intake are highly variable.

In the United States, dietary fiber intake was calculated to be 17 g for males and 12.8 g for females based on the NHANES III study [322]. Based on the results of the Nationwide Food Consumption Survey, a mean dietary fiber intake of 11.4 g per day was reported [323]. Similarly, a mean daily fiber intake of 13.7 g in total, comprising 4.2 g of water-soluble fiber and 6.8 g of water-insoluble fiber, was described based on the Multiple Risk Factor Intervention Trial [324]. In contrast, Hallfrisch et al. [325] and Hermann et al. [326] reported higher intake values, averaging 15 g/day and 18.3 g/day, respectively. Regardless, intakes of dietary fibers in the American population are below levels recommended by the Institute of Medicine (38 g for males and 25 g for females).

In Canada, low daily dietary fiber intakes have been also noted. According to Nova Scotia Department of Health [327], the mean dietary fiber intake was estimated to be 13.5 g per day, ranging from 9.6 g (young women) to 17 g (elderly men). The main sources (88%) of fiber in the diet were reported to be pasta, rice, cereals and breads, vegetables, fruits, and fruit juices [327]. Similarly, in a more recent study on healthy Canadian adolescent males, a median dietary fiber intake of 13.1 g per day was observed [328].

In Europe, the estimated national values for dietary fiber intake were found to fall within a narrower range: 16 g/day in France [329], 22.1 g/day in Sweden [330], 16.7–20.1 g/day in Finland [331], 21 g/day in Germany [332], and 20–22 g/day in the Netherlands [333]. An exceptionally high intake level of fiber was found in Switzerland, 30–33 g/day, reflecting a positive trend in the eating habits of this population [334]. In the United Kingdom, lower values of 14–16 g/day for men and 18-19 g/day for women were reported [335].

Thus, fiber intakes worldwide are well below the recommended levels despite the recommendations of several health organizations to increase the consumption of foods with high fiber content.

4.2. Beta Glucan in Functional Foods. The introduction of fiber into traditional and processed foods provides one method by which to increase fiber intake [81]. Based on consumers' demands for healthier options, the food industry has aimed at developing new products towards functional foods and ingredients.

The best-known examples of functional foods are fermented milks and yoghurts. Several fiber-fortified dairy products are now appearing in market, with inulin being a popular fiber source for such products due to its combined nutritional and technological characteristics [336–341].

Beta glucan is commonly used as a functional ingredient in foods as it is readily available as a byproduct of oat and barley milling and it also provides physiological benefits that are supported by health claims in many jurisdictions. This polysaccharide is also used as a food ingredient in the form of hydrocolloids [342, 343] or as powder using microparticulation [344]. The addition of β-glucan into various products, such as baking products, muffins, cakes, pasta, noodles, muesli cereals, milk products, soups, salad dressings, beverages, and reduced-fat dairy and meat products, was found to affect their attributes, including bread making performance, water binding and emulsion stabilizing capacity, thickening ability, texture and appearance, in a concentration-, molecular weight-, and structure-dependent manner [22, 345, 346]. Besides enhancing the nutritional value, β-glucans can improve the sensory and gustatory properties of some products. However, the stability of the physiological properties of β-glucan when extracted and added to foods has received little examination, leaving uncertain the health benefits of β-glucan when incorporated into foods.

In the following sections, the chemical and physiologic functionality of β-glucans in food preparations is discussed.

4.2.1. Breakfast Cereals. Oats have been frequently used as an additive in the preparation of cereal products, decreasing water activity and subsequently prolonging durability [81]. Several oat-based breakfast cereals have experienced great success in the market. Adding 20% oat β-glucan into chocolate breakfast flakes protected the viability and stabilized the cells of *lactobacillus rhamnosus*, a gut-friendly probiotic bacteria, at temperatures higher than 20°C [347]. As breakfast cereals are commonly consumed in North America, several oat-based hot and cold breakfast cereals are available in the market, making use of β-glucan's approved health claims. These products are readily accepted by consumers.

4.2.2. Baking Products. The incorporation of oats into baking products, such as bread, baked goods, and dough, has

been widely tested [81]. The incorporation of β-glucans to baking products seems promising, ameliorating both sensory characteristics and health properties of products at a maximum concentration of 20%. When oat flour has been substituted for 10% of fine wheat flour in bread, product quality improved in terms of crust color, bread softness, and taste [348]. Moreover, a positive effect of oat β-glucan on the sensorial characteristics of biscuits has been described [343]. The addition of the hydrocolloids Nutrim O-B (10% β-glucan) and C-Trim-20 (20% β-glucan) increased the taste, moisture, and adhesiveness of the product. Similarly, an oat component called Nutrim-5, a hydrocolloid preparation of β-glucans produced by treating oat grain or flour with a thermal process, improved the overall strength of pasta without negatively affecting either the quality or the sensory properties [349].

4.2.3. Milk Products. Oats are also used as additives in the production of yogurts with increased amount of fiber [81]. Fiber addition increased the solidity ratio and texture of unsweetened yogurts, accelerated their acidification rate, and increased their viscosity [350]. When substituting fat with β-glucans hydrocolloid component at 3.47% and 6.8% in low-fat cheddar cheeses, a softer texture was described with decreased melting time and lowered sensory properties [351]. The addition of oat β-glucans concentrate, at 0.7% and 1.4% w/w, to white low-fat cheese products in salt brine improved product texture, while unfavorably affecting its appearance, taste, and odor when compared with the control samples [352]. The probiotic effect of β-glucans has been also studied. Beta glucans selectively support the growth of *Lactobacilli* and *Bifidobacteria,* both of them being antagonists to pathogenic bacteria in the digestive system [12, 173]. The addition of oat β-glucans to probiotic milk-based drinks, at doses of 0.31–0.36%, increased their stability along with their health benefits [353].

The effects of β-glucan on milk sensorial properties have been reported, but results are variable [56, 121, 245, 354]. Oat milk containing β-glucan (0.5 g/100 g) was well perceived and got similar sensory evaluation as the control drink (<0.02 g β-glucan/100 g) [56]. Sensory evaluations were higher for the milk beverage (500 mL) enriched with 5 g as compared to the one enriched with 10 g of oat and barley β-glucan [121]. However, milk enriched with 5 g β-glucan had similar sensorial characteristics to the control drink.

In conclusion, the addition of β-glucans to yogurts seems to impair their sensory qualities despite improving other rheological properties, irrespective of the dose. On the other hand, addition of β-glucans to milk, at doses not exceeding 1%, may provide health benefits without compromising sensorial attributes.

4.2.4. Meat Products. Due to its ability to mimic fat characteristics, oat fiber is one of the most effective ingredients in making low-fat meat products. It can be used to offset the poor quality associated with low-fat beef burgers [355] as well as low-fat sausages [356]. There is no specific study investigating the effect of β-glucan, as a fat replacer, on the sensorial attributes and rheological properties of meat products. Thus, future studies should address this applicability option of β-glucan.

In conclusion, the introduction of β-glucans into food preparations has both beneficial and deleterious impacts. Such impacts mainly depend on the food product to which β-glucan is added, in addition to the source, the form, and the dose of β-glucan in use. Alterations in the sensorial properties and physiochemical attributes induced by β-glucan may be desirable for some products while being detrimental for others.

4.3. Challenges of Beta Glucan Fortification. One of the major challenges faced by the functional food industry is developing functional foods with an acceptable taste to the average consumer [357]. Incorporating significant quantities of fiber into food products constitutes a technological challenge due to the possible deleterious effects on textural quality. The addition of fibers may contribute to modifications in the texture, sensory characteristics, and shelf-life of foods due to their water-binding capacity, gel-forming ability, fat mimetic, antisticking, anticlumping, texturising, and thickening effects [358, 359].

Adding β-glucan into milk and dairy products was reported to be problematic; first due to its viscosity that may alter the sensory characteristic of foods and second due to its typical slimy texture in the mouth [100]. However, the acceptance rate does not seem to be influenced by the amount of β-glucan added to test products but rather by the duration of consumption of these products. Blackcurrant flavored oat milk (0.5 g β-glucan/100 g) was well liked among volunteers without differencing it from its counterpart, a rice beverage with the same flavor (<0.02 g β-glucan/100 g), at a single evaluation [56]. In addition, the sensory quality of a flavored oat-based fermented product (containing 0.6% β-glucan) was acceptable, in comparison to flavored commercial yogurt or nondairy products, in one single taste test [354]. In contrast, when consumed over 5 weeks, oat-based fermented dairy products (0.5-0.6% β-glucan) were less preferred than fermented dairy-based control products (<0.05% β-glucan) [245]. Similarly, after a period of 5 weeks, beverages with 10 g of barley or oat β-glucan were rated lower than those with 5 g of barley or oat β-glucan [121]. These findings reflect that, when chronically consumed, β-glucan may impair the sensorial perceptions of foods.

Thus, the development of β-glucan-fortified foods remains highly challenging as consumers are not willing to accept greater health benefits on the expense of deteriorations in the sensory characteristics of food products.

4.4. Effects of Food Processing on the Biological Activities of β-Glucan. Food processing alters the physical, chemical, and physiologic characteristics of dietary fibers. Several processing techniques, including cooking, freezing, and storing, affect the physicochemical characteristics of β-glucan. Both molecular weight and extractability are important components of the physiological activity of β-glucan and both can be affected by food processing [360]. The molecular weight

of β-glucan in processed oat foods can be smaller than unprocessed. Solubility, which is related to extractability, typically increases initially with processing as depolymerisation occurs and β-glucan is released from the cell wall; however, as this degradation continues, solubility decreases as insoluble β-glucan aggregates are formed [361]. In products such as oat porridge and oat granola, there is little effect of processing on β-glucan molecular weight [172, 362]. However, the molecular weight of β-glucan in products such as oat crisp bread decreases by 92% compared to its original oat source [362]. Other studies have also seen reductions in molecular weight in similar products made from different grains [168, 172, 363] and attributed these reductions in molecular weight to the effects of β-glucanase enzymes in wheat flour used to make these products [168, 172, 364–366]. These reductions in molecular weight increase with the mixing and fermentation time of the dough [172]. Freezing was also found to affect β-glucan solubility. Frozen storage of oat bran muffins significantly lowered β-glucan solubility over time, using *in vitro* extraction simulating human digestion [231]. In addition, freeze-thaw cycle reduced the solubility of β-glucan in oat bran muffins by 9% to 55% of the fresh values.

Whether such physicochemical alterations induced by food processing have a significant impact on the established health properties of β-glucan is not clear. Effectiveness of β-glucan in modulating glucose and insulin parameters is related to dose and viscosity, which can be altered during processing [74]. In fact, 85% of the variation in blood glucose concentrations is explained by the amount of β-glucan solubilized and not the total amount originally added to food [367]. On the other hand, the role of viscosity, molecular weight, and solubility, susceptible to modifications by food processing, in regulating β-glucan's effect on cholesterol metabolism has not been demonstrated and requires further investigation [74].

Thus, since physiologic effects of β-glucans may be altered by food processing, it is important to develop a further understanding of such an interaction.

5. Summary and Conclusion

It is clear that β-glucan is an important food component in the modulation of metabolic dysregulations associated with the metabolic syndrome. However, dose, form, molecular weight, and the carrier food of β-glucan shape its effect. The physiological effects of β-glucan are mainly attributed to its physicochemical and structural characteristics interacting with the gastrointestinal tract, as reflected by its ability to generate viscous solutions at low concentrations in the upper part of the gastrointestinal tract and to undergo fermentation in the colon.

Although the physiological effects of ingested β-glucan are similar to other soluble fibers, its availability and ease of handling leads it to be increasingly incorporated into foods with the purpose of increasing daily fiber consumption. However, challenges in incorporating β-glucan into some food items without compromising their sensorial properties and their acceptance by consumers do still exist, and need to be resolved.

Conflict of Interests

D. El Khoury, C. Cuda, B. L. Luhovyy, and G. H. Anderson declare that there is no conflict of interests.

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Research Article

Effects of a Cereal and Soy Dietary Formula on Rehabilitation of Undernourished Children at Ouagadougou, in Burkina Faso

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The New Misola consists of millet soybean, peanut, vitamins, minerals, and industrial amylase. Our objective is to demonstrate that porridge made from local grains and legumes restores the nutritional balance of malnourished children. The study was carried on 304 malnourished children aged 6–48 months including 172 girls and 132 boys from Saint Camille Medical Centre. At the beginning, these malnourished children had a WHZ z-score of -3.10 and a WAZ z-score of -3.85, which reflected, according to WHO, a severe malnutrition. After eight weeks of nutritional rehabilitation, a normal WHZ of -1.41 was obtained. These children recovered more than those in a similar study performed in 2006 with the old formula of Misola. This study shows that malnutrition remains a public health problem in Burkina Faso. It should be necessary that public health services and the epidemiologists work in synergy with nutritionists and "*nutrigenetics*" in order to combat malnutrition efficiently.

1. Introduction

Malnutrition is a major public health problem. Indeed, undernutrition affects several millions of people worldwide, mainly children under five years. FAO estimates that a total of 925 million people are undernourished in 2010 compared with 1.023 billion in 2009; that is higher than before the food and economic crises of 2008-2009 and higher than the level that existed when world leaders agreed to reduce the number of hungry by half at the World Food Summit in 1996 [1]. Thus, in developing countries, nearly one in five is undernourished, while, in Africa, it is one in three. In West Africa, many studies report that, in hospitals, children with severe malnutrition have a mortality rate of 20% compared to 4% for those who are not [2, 3].

Malnutrition is a condition resulting from deficiency or excess of one or more essential nutrients. Undernutrition that occurs most often in developing countries leads in children under 5 years to stunting or delayed growth, emaciation, and underweight. It mainly causes diseases such as marasmus and kwashiorkor [4]. Overnourishment causes obesity, diabetes, and high cholesterol, and undernutrition is a risk factor for cardiovascular disease [5].

Like other Sahelian countries, Burkina Faso is confronted each year with significant risks for food security and nutritional deficiencies. Malnutrition represents 1/3 of the direct and indirect causes of child mortality at pediatric age. In Burkina Faso, prevalence of acute diseases linked to nutritional deficiencies was 21.2% in 2003 [6], while in 2009 chronic malnutrition rate in children less than 5 years was 35.1%, which constitutes more than 330,000 children suffering from acute malnutrition and over 1,000,000 children with chronic malnutrition [7].

For many children, lack of access to enough food is not the only cause of malnutrition. The lack of nutritional

quality, poor feeding practices, and parasitic, bacterial, and viral infections act synergistically in the worsening and aggravation of the nutritional problems [8, 9]. However, primitive man lived basically on picking and hunting and fed mainly on vegetables, fruits, and grains he met on his way. Despite this food insecurity, he found solutions to nutritional problems in nature. Today, with the introduction of cash crops at the expense of food crops, overexploitation of soils due to overpopulation, industrialization, urbanization, and the development of slums and suburbs adjacent to large cities, children from poor families live in a nutritional imbalance.

The management of cases of severe malnutrition in developing countries through the use of porridges composed of flour of local grain and legumes in order to restore nutritional balance for the infant is today a priority target for developing countries. In this purpose, for over 15 years, in the Center for Recovery and Nutritional Education (CREN) of the Saint Camille Medical Centre (CMSC), each year, almost 800 malnourished children with marasmus (M), kwashiorkor (K), or both (M, K) have been nutritionally recovered thanks to a porridge prepared from local grains and legumes: *Pennisetum glaucum* (millet), *Soja hispida* (soja), *Arachis hypogaea* (peanut). This porridge is prepared from a flour called "Misola" whose production, in Burkina Faso, is supported by a nonprofit organization: the Burkinabe Association of Misola Units.

Phytochemical and biochemical studies of Misola flour show that it contains different types of proteins, glucoses, and carbohydrate elements that promote nutrition and human health [4]. From 2010, a change has occurred in the composition of the flour Misola. The New Misola (NM) is enriched with vitamins, minerals, and industrial amylase. In addition, in this new flour, the amount of sugar has risen from 2.5 kg to 3.5 kg for 25 kg.

The main objective of this study was to demonstrate that the porridge made from local grains and legumes can help to restore nutritional balance. It is in this purpose that the New Misola was used in the CMSC to save malnourished children suffering from marasmus or kwashiorkor, or both.

The specific objectives of this research were to (i) search for causes of malnutrition in the city of Ouagadougou, (ii) estimate, from the anthropometric parameters of malnourished children, the degrees of severity through z-scores calculations, (iii) use the New Misola to recover nutritionally malnourished children, and, finally, (iv) compare the results of this study that used the New Misola (NM) with those of the study carried out in 2006 on the old formula of Misola.

2. Subjects and Methods

2.1. Study Patients. The study was conducted in the CREN (Center for Recovery and Nutritional Education) of Saint Camille Medical Centre (CMSC), where about 800 malnourished children are followed every year. The study recruited all the 310 malnourished children attending this CREN from November 2010 to April 2011. Among them, 304 children, aged 6 to 48 months (average age 13.84 ± 6.68 months) including 172 girls and 132 boys, have followed the protocol of nutritional rehabilitation for 8 weeks. For 6/310 children, we stopped the research protocol because their health status required a reference to the national pediatric hospital. Among the 304 children no death was observed during the eight weeks of nutritional rehabilitation.

At the beginning of this study, undernourished children were anorexic and many of them had diarrhea and were treated with nose-gastric (NG) rehydration according to the CMSC protocol [10]. They were taken off NG feeding before being selected for this study, since this condition had sufficiently improved to allow moving on to oral feeding. Criteria of exclusion were refusal to participate in the study, while criteria of discontinuation of participation were abandonment, death, and the interruption of treatment at the centre during the study. All studied children were undernourished according to the z-score criteria, recommended by WHO and UNICEF: (i) z-score inferior or equal to -3 standard difference corresponds to severe malnutrition; (ii) z-score between -3 standard difference and -2 standard difference corresponds to moderate malnutrition; (iii) z-score greater than -2 standard difference corresponds to a normal nutritional status. The ages of undernourished children were confirmed by their birth notebooks.

2.2. Anthropometric Parameters. Weight, height, brachial perimeters (BPs), and head perimeters (HPs) of the children were recorded. The weight of the children was recorded once a week from the day of admission to the CREN with a 10-gram sensitivity balance. The brachial perimeter (BP) is the mid-upper-arm circumference (MUAC). It is measured at the midpoint between the tips of the shoulder and elbow using an MUAC tape. The MUAC of children aged 6–59 months shows the degree of malnutrition: BP < 11.0 cm indicates severe acute malnutrition; 11.0 cm < BP < 12.5 cm corresponds to a moderate malnutrition; 12.5 cm < BP < 13.5 cm corresponds to a risk of malnutrition; 13.5 < BP corresponds to a satisfactory nutritional status [11].

The measure of head circumference (head perimeter); in children, head growth has been used by healthcare providers as a marker of brain well-being, because an abnormal rate of growth could suggest a pathological disorder requiring diagnosis and possible treatment, for example, hydrocephalus, psychosocial problems, and craniosynostosis. Measure Head Circumference as the name implies, occipital frontal circumference (OFC) is a measurement of the circumference of the head around the occiput, or posterior aspect, of the skull, to the most anterior portion of the frontal bone. An accurate head circumference measure is obtained with a flexible nonstretchable measuring tape [12]. The height of children <2 years was measured by resting the child in the supine position; in those children >2 years, height was measured in the upright position (as described by Simpore et al. [13]). The nutritional status, evaluated by brachial perimeters, was compared to Jelliffe's classification [14], considering that it varies little for children <4 years. HAZ (height for age z-score), WHZ (weight for height z-score), and WAZ (weight for age z-score) parameters were calculated according to the references of the National Center for Health Statistics (NCHS) [15]. At the CMSC, numbers from 1 to 4 drawn

Table 1: Parents' jobs, educational level.

	Occupation					Level of training	
	Traders	Handicraft	Wage-earner	Housewife	Pupil	Illiterate	Literate
Father	272	20	12			261	43
	89.47%	6.58%	3.95%			86.86%	14.14%
Mother	24	14		264	2	284	20
	7.89%	4.61%		86.84%	0.66%	93.42%	6.58%

from the norms of Stuart and Stevenson [16] are used as measures to show the stages of severity of malnutrition. The number 1 is the primitive stage (M1 or K1), number 2 shows a moderate stage (M2 or K2), number 3 shows the severe stage (M3 or K3), and number 4 shows a very severe stage (M4 or K4).

2.3. Evaluation of Results. The evaluation of the nutritional status of the children has been made according to the nutritional indices (as described by Simpore et al., [4]). The weight for age index expressed in z-score (WAZ) or weight insufficiency indicates a global malnutrition affecting both the linear growth and the weight increment. The height for age index expressed in z-score (HAZ) or growth delay is an index indicating chronic malnutrition provoked by an extended reduction of food consumption and by repeated pathologic episodes. Emaciation or weight loss expressed by the weight for height index (WHZ) indicates a slightly less malnutrition status or weight deficit due to a decrease or slowdown of regular growth.

2.4. Preparation and Administration of the New Misola (NM). The flour is produced by the handicraft production unit (Unité de Production Artisanale: UPA) of the CMSC, which has been operating since 1998 and is part of the network of UPAs acknowledged by the Misola Association (http://www.misola.org), which is responsible for the quality control of the product every year.

The mothers of the undernourished children fed on New Misola (NM) were given weekly rations of 1500 grams, three bags, each containing 500 grams of flour. The daily quantity in grams of MN porridge to provide to children with malnutrition is obtained by the following formula: $(P + 250)/4$, where "P" is the weight in decagrams. This formula is done by the Misola Association. We specify that the Misola is a dietary supplement it is not a substitute for breastfeeding which is highly recommended for malnourished young children. The NM flour is a mixture of millet, soya, peanut kernel, sugar, salt, vitamins and industrial amylase. In 100 g of NM used, we have 405 kcal of energy, 16.8 g of proteins, 10.1 g of lipids, and 63 g of carbohydrates, minerals, and vitamins. The preparation of the NM was carried out according to traditional customs, namely, 60 grams of flour and 200 mL of water were mixed and boiled over a low fire, mixing for 5-6 minutes. Each mother has to cook it, 4 times a day (6:30, 10:30, 14:30, and 18:30), in order to feed her child. After this preliminary phase they continued to administer the mixture at home. Each day they accompanied their children to the CREN to monitor weight and other anthropometric parameters and deliver the 24-hours diet recall sheet to CREN (as described by Simpore et al., [4]).

2.5. Survey. The parents of the malnourished children have freely agreed to answer a questionnaire relating to their jobs, their educational level, and number of children living and deceased.

2.6. Statistical Analysis. Demographic and clinical profile were memorized in Excel sheet and analyzed by standard software SPSS-17 and EpiInfo-6. Statistical significance was set at $P < 0.05$. The Chi^2 test was used to compare the proportions of different parameters of the study, whereas the t-test was used to compare the nutritional status of children in the 2006 survey with those of 2011.

3. Results

This study was carried out on 304 undernourished children utilizing New Misola. Table 1 shows the information on the occupation and the level of school training of the parents of these undernourished children. We note that 284 (93.4%) mothers were illiterate and only 12 (3.95%) fathers were integrated in the public service. In this study, 264 (86.8%) mothers were housewives.

Table 2 presents the different kinds of malnutrition: 92.43% of these children had marasmus, a severe malnutrition (M3), and 2.30% had moderate grade marasmus (M2) at the beginning of the investigation. The number of malnourished children at M3 decreases significantly with age: the age group number 1 (36.65%); number 2 (32.03%); number 3 (14.23%).

Table 3 shows the biochemical composition for 100 grams of used Misola at the CMSC. The lipid composition is represented by palmitic, linoleic, oleic, γ-linolenic, stearic and palmitoleic acids [4].

Males' age, weight, height, head perimeter (HP), and brachial perimeter (BP) were greater than females with respective significance: $P = 0.115$ (NS), $P = 0.002$, $P < 0.001$, $P < 0.001$, and $P = 0.061$ (NS) (see Table 4).

Table 5 compares the anthropometric parameters (age, weight, height, and brachial perimeter (BP)) of this research with those of Simpore et al. [4]. In all parameters, we have differences that are statistically significant: age ($P = 0.004$), weight ($P = 0.013$), height ($P = 0.004$) and BP ($P < 0.001$).

Table 2: Different kinds of malnutrition with the 304 children according to the age groups.

Age group	Months	M1	M2	M3	K1	K2, M3	Total
1	6 to 9	2/4	2/7	103/281	2/3		109/304
		50.00%	28.57%	36.65%	66.67%		35.85%
2	10 to 14			90/281	1/3	2/9	93/304
				32.03%	33.33%	22.22%	30.59%
3	15 to 19		5/7	40/281			45/304
			71.43%	14.23%			14.80%
4	20 to 48	2/4		48/281		7/9	57/304
		50.00%		17.09%		77.78%	18.75%
	Total	4	7	281	3	9	304

$\chi^2 : 1 \to 2$; $P = 0.248$, $\chi^2 : 1 \to 3$; $P < 0.001$, $\chi^2 : 1 \to 4$; $P < 0.001$, $\chi^2 : 2 \to 3$; $P < 0.001$, $\chi^2 : 2 \to 4$; $P < 0.001$, $\chi^2 : 3 \to 4$; $P = 0.353$.
M1: marasmus phase 1; M2: marasmus phase 2; M3: marasmus phase 3; K1 and K2: Kwashiorkor phases 1 and 2.

Table 3: Biochemical composition of Old Misola (OM) and new Misola (NM) produced at Saint Camille Medical Centre.

Biochemical composition	Old Misola	New Misola
Protein (g)	15	16.8
Lipid (g)	11	10.1
Glucides (g)	61	63
Added sugar	10% of the formula	13% of the formula
vitamins	—	0.8% of the formula
minerals	3 g	0.8% of the formula
Amylase	Germinated sorghum flour	800 mg Industrial Amylase[1]
Calories/kcal/100 g	425	405

[1] Amylases are enzymes that hydrolyze starch, that is, fragment chains cooked starches to provide soluble sugars. We switch from a thick consistency to a liquid without loss of nutrients. Amylase in the liquefaction has nothing in common with the dilution with water. The slurry becomes sweeter.
Amylases can be obtained locally from germinated cereals: malt sorghum, millet, or corn.
Indeed, we used to germinate the seeds and produce amylase, but this product was quickly spoilt by heat. That is why we are using industrial amylase now, as it is stable.
Dried, ground, and sieved, the malt is added in very small quantities in the hot porridge after cooking (as it is partly destroyed by heat).
The malt can also be added to the flour before cooking, but it is then necessary to add ten to fifteen times more. Amylase industry is not destroyed by cooking and is very powerful. Thus, it can be incorporated into the flour, in minute quantities before cooking.

Table 6 shows the anthropometrics parameters of the children at the beginning and at the end of our study and those of Simpore et al., [4]. In this research, the z-scores identified at the beginning of the study and those of the end have statistic difference significance: WHZ1 versus WHZ2 ($P < 0.001$) and WAZ1 versus WAZ2 ($P < 0.001$). It was also found statistic difference significance when comparing z-scores from this study and those of Simpore et al., [4]: WHZ1 versus WHZ1 ($P < 0.001$); WAZ2 versus WAZ2 ($P = 0.033$). We do not consider the parameters size and age (HAZ) because the study lasted two months and the sizes of the children have not increased significantly.

Table 7 reveals that, before the nutrition rehabilitation, (55.26%) 168 of malnourished children had WHZ < -3 and therefore a severe condition. After 8 weeks of nutritional rehabilitation, there was only (06.58%) 20 children with WHZ < -3 and (63.81%) 194 children have progressed with a normal WHZ > -2. Similarly, for WAZ, we had (85.53%) 250 children who had a WAZ < -3, and, after nutritional rehabilitation, there was only (38.16%) 116 children with WAZ < -3.

4. Discussion

The New Misola (NM) we have used for the nutritional rehabilitation of the children was composed of 60% of small millet, 20% of soya beans, and 10% of groundnuts which contain proteins, glucose, and lipids. Moreover, it had been enriched with vitamins, carbohydrates, minerals, and industrial amylase.

Treatment compliance was excellent, and none of the children dropped out. The mothers reported that the children accepted the meal of NM. They attended weekly appointments, but only the first and the last visit (8 weeks) were considered in the final evaluation.

After eight weeks of study, children treated with NM, appeared clinically improved; their weight increased. This study enabled us to show that the malnutrition of pediatric aged children is directly related to the level of their parents' level of education and their occupation. In fact, most of their mothers were illiterate (93.42%) and housewives (86.84%) while only 14.14% of their fathers were literate and 3.95% had a monthly salary. Moreover, their parents had several other children (41.4% of mothers had more than 3 living children), and some of them were even deceased. Emphasize that 20.4% of parents had at least one child died and 7.2% had more than 3 children died. These elements could reveal family penury and poverty which would partly account for such malnutrition of the living children when they are less than 5 years old (Table 1). But we have no statistical data

Table 4: Median anthropometric parameters of the 304 children according to sex at beginning and at the end of the study.

	Females (172)			Males (132)			All children (304)			
Parameters	Initial mean	End mean	*P*: I → E	Initial mean	End mean	*P*: I → E	Initial mean	End mean	*P*: I → E	*P*: Females_i → Males_i
Age (months)	13.31 ± 6.64	15.73 ± 6.53		14.53 ± 6.72	16.82 ± 6.53		13.84 ± 6.68	16.20 ± 6.53		
Weight (kg)	5.64 ± 1.29	7.28 ± 1.43	<0.001	6.10 ± 1.27	7.88 ± 1.45	<0.001	5.84 ± 1.30	7.54 ± 1.47	<0.001	0.002
Height (cm)	68.78 ± 6.16	70.2 ± 6.21	0.134	70.85 ± 6.26	72.71 ± 6.05	0.085	69.68 ± 6.27	71.29 ± 6.25	0.026	0.004
HP (cm)	42.02 ± 2.06	43.14 ± 2.16	0.001	43.23 ± 2.10	44.30 ± 1.86	0.002	42.55 ± 2.16	43.65 ± 2.11	<0.001	<0.001
BP (cm)	10.46 ± 1.10	12.66 ± 0.91	0.001	10.71 ± 1.21	12.7 ± 0.93	0.001	10.57 ± 1.15	12.68 ± 0.91	<0.001	0.061

BP: brachial perimeter; HP: head perimeter.

Table 5: Anthropometric parameters according to the two studies.

Parameters	2011 study			2006 study			t-test: ^ → *: P
	Females (172) Mean	Males (132) Initial mean	All children (304)^	Females (286) Mean	Males (264) Initial mean	All children (550)*	
Age (months)	13.31 ± 6.64	14.53 ± 6.72	13.84 ± 6.68	15.64 ± 8.08	15.01 ± 6.87	15.30 ± 7.41	0.004
Weight (kg)	5.64 ± 1.29	6.10 ± 1.27	5.84 ± 1.30	5.82 ± 1.17	6.28 ± 1.36	6.07 ± 1.29	0.013
Height (cm)	68.78 ± 6.16	70.85 ± 6.26	69.68 ± 6.27	68.07 ± 6.13	68.43 ± 7.48	68.27 ± 7.13	0.004
BP (cm)	10.46 ± 1.10	10.71 ± 1.21	10.57 ± 1.15	10.75 ± 1.13	10.99 ± 1.25	10.88 ± 1.20	<0.001

BP: Brachial perimeter.

Table 6: Nutritional status at the beginning 1 and end of the study 2.

	304 children with New Misola 200 g/day, 2011	170 children with Misola 200 g/day [4]	P
WHZ1 1 → 2	−3.10 ± 0.94	−1.73 ± 2.51	<0.001
	$P < 0.001$	$P = 0.035$	
WHZ2	−1.41 ± 1.08	−1.14 ± 2.64	0.118
WAZ1 1 → 2	−3.85 ± 0.87	−4.01 ± 0.98	
	$P < 0.001$	$P < 0.001$	0.067
WAZ2	−2.75 ± 0.89	−2.95 ± 1.12	0.033

WHZ1, WAZ1: z-scores of the beginning; WHZ2, WAZ2: z-scores of the end.
WHZ1: weight for height z-score at beginning of the study; WHZ2: weight for height z-score at the end of the study; WAZ1: weight for age z-score at the beginning of the study; WAZ2: weight for age z-score at the end of the study.

indicating that these dead children have died from malnutrition. In addition we know that other studies have shown that, among malnourished children, some had viral infections (rotavirus, adenovirus, HIV) [17], bacterial and parasitic infections that cause diarrhea and dehydration, leading them to death.

We notice that the majority of these children were in stage M3 which corresponds to a severe marasmus (Table 2). At the beginning of the study the malnourished children had a z-score of weight and height WHZ = −3.10 and a z-score of weight and age WAZ = −3.85 which meant, according to the WHO criteria, a severe malnutrition (Table 6). According to the z-score WHZ, the children of this study were much more malnourished than those of Simpore et al. in 2006 [4] (−3.10 ± 0.94 versus −1.73 ± 2.51) with $P < 0.001$.

However, eight weeks after their nutrition with New Misola, we score a normal WHZ of −1.41 which is similar to the results obtained by Simpore et al. [4] ($P = 0.118$). Other studies carried out on malnourished children with other foods, such as that [18] of Ekpo et al. Abidoye and Nwachie, [19], and Kwena et al., [20]. With this study, in 8 weeks, the children have recovered 1700 grams or 30.36 grams/day, whereas, in the study by Simpore et al. [4], children recuperated 20 grams/day. Now, when we consider the WAZ, our children had the same level of emaciation as for the study carried out by Simpore et al., [4] ($P = 0.067$). Nevertheless, the children in this study had recovered more than those of Simpore et al. [4] ($P = 0.033$). That could be caused by the addition of vitamins, minerals, and industrial amylase in the Misola flour.

The flour of the New Misola is basically composed of millet, soya beans, and groundnuts as detailed previously. Apart from the proteins, glucose, and lipids, millet is a grain that contains microelement such as magnesium, calcium, iron zinc, copper, and manganese. Groundnuts contain glucose, protides, lipids, sodium, potassium, manganese, calcium, iron, zinc, and so forth, while soya beans contains calcium, iron, magnesium, phosphorus, potassium, sodium, vitamins (A, B1, B2, B3, B5, B6, B12, C, E), folic acid, linoleic acid, alpha-linolenic acid, isoflavone, and so forth.

The inflationary trend, "the cost of living" in Burkina Faso, makes it almost impossible for many poor families to afford animal protein from meat, fish, and egg for their children. This has led us to the search for an alternative (vegetable protein) to animal protein in human diets. The use of plant protein can serve as a complement to animal protein in human diets so as to increase the total protein intake [21]. Among the plant protein sources, soya beans is identified as one of the best because of its relatively high protein content and amino acid profile that is only low in sulphur-containing amino acids [22]. Several studies have shown that soybean can be grown in almost all parts of West Africa [23–25]. The regular consumption of the Misola porridge which contains soya beans helps to complement, in the undernourished children, the low intake of animal protein.

Therefore, we understand the reason why the New Misola porridge can nutritionally rehabilitate undernourished children. The Misola, through its elements of composition (zinc, iron, and selenium), could reestablish also in the

Table 7: Percentage of nutritional rehabilitation of children according to z-scores.

Stage	WHZ			WAZ		
	WHZ1	WHZ2	P	WAZ1	WAZ2	P
z-score > −2	32 (10,53%)	226 (74,34%)	<0.001	0 (0%)	64 (21,05%)	—
−3 < z-score < −2	104 (34,21%)	58 (19,08%)	0.035	44 (14,47%)	124 (40,79%)	<0.001
z-score < −3	168 (55,26%)	20 (06,58%)	<0.001	260 (85,53%)	116 (38,16%)	<0.001

WHZ1: weight for height z-score at beginning of the study; WHZ2: weight for height z-score at the end of the study; WAZ1: weight for age z-score at the beginning of study; WAZ2: weight for age z-score at the end of the study.

malnourished children the depressed immune system [26, 27].

5. Conclusion

This study shows that malnutrition remains a public health problem in Burkina Faso and over the world. The consequences of malnutrition represent a global problem, which affects morbidity as well as mortality. Awaiting the enrolment of these undernourished children in rehabilitation protocols, those in charge of public health services and epidemiologists should work in synergy with nutritionists and nutria-genetics in order to combat malnutrition efficiently [4]. According to the instructions that the mothers received, involvement of the families of the undernourished children and of the whole community is essential to control the great prevalence of malnutrition in African countries.

Indeed, whole grains and legumes bring to the human being energy and the needed micronutrients for his or her metabolic homeostasis. Without the external contribution of these fundamental elements produced by these vegetables, the human being would be unable to synthesize them for his or her own metabolic processes. At the present time of globalization, the world seems to have become a big village. The kitchens of the international community must review their diet by basing them upon grains and legumes that are sources of a sound nutrition. Moreover, it would be very important to promote the science of nutrition and to develop the nutria-genetics science in order to cast new foundations of nutrition for the future, taking into account the requirements of population's genetics.

Ethical Committee

The Ethics Committee of the Saint Camille Medical Centre approved this protocol of study and authorized each person, after oral consent, to accept this study.

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Review Article

Whole Grains, Legumes, and the Subsequent Meal Effect: Implications for Blood Glucose Control and the Role of Fermentation

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Whole grains and legumes are known to reduce postprandial glycemia and, in some instances, insulinemia. However, the subsequent meal effect of ingesting whole grains and legumes is less well known. That is, inclusion of whole grains or legumes at breakfast decreases postprandial glycemia at lunch and/or dinner on the same day whereas consumption of a whole grain or lentil dinner reduces glycemia at breakfast the following morning. This effect is lost upon milling, processing, and cooking at high temperatures. The subsequent meal effect has important implications for the control of day-long blood glucose, and may be partly responsible for the reduction in diabetes incidence associated with increased whole grain and legume intake. This paper describes the subsequent meal effect and explores the role of acute glycemia, presence of resistant starch, and fermentation of indigestible carbohydrate as the mechanisms responsible for this effect.

1. Introduction

Whole grains are those that contain intact cereal germ, endosperm, and bran. Whole grain intake is associated with a variety of beneficial health effects. In large epidemiological studies, whole grain intake is associated with lower body mass index (BMI) [1], and lower incidence of type 2 diabetes, cardiovascular disease [2, 3], and colorectal cancer [4]. Likewise, legume consumption is associated with a reduction in the incidence of type 2 diabetes [5] and, in small prospective intervention studies, with increased glucose tolerance and improved lipemia [6]. One of the mechanisms that may be responsible for the beneficial effects of whole grain and legume consumption is their ability to lower postprandial glucose and insulin responses which, in turn, has effects on hepatic and lipid metabolism [7]. Although the ability of certain whole grains and legumes to lower postprandial glycemia is well documented [8, 9], little attention has been given to the subsequent meal effect of whole grain and legume ingestion. The subsequent or second meal effect is the ability of whole grains and legumes to lower postprandial glycemia not only after the meal at which they are consumed but also at a subsequent meal later in the day or even on the following day. This effect could be useful for blood glucose control in diabetic patients but could also confound insulin dosing regimens by causing an uncalculated or unexpected decrease in insulin requirements at the subsequent meal.

Whole grains and legumes are a collection of different foods with differing structural and physicochemical properties. The amount of insoluble fiber, resistant starch, phytochemicals, granule size, porosity, the interaction of starch and protein within the structural matrix, and other bioactive compounds differs amongst different whole grains and legumes so it is important to examine the effect of different foods on day-long glycemia. Also, given these different properties, it is possible that different whole grains and legumes could possess distinctly different mechanisms of action with regard to the subsequent meal effect. These ideas will be explored in this review, the purpose of which is to describe the subsequent meal effect as it pertains to consumption of whole grains and legumes, discuss the implications for blood glucose control on long-term health, and examine the possible mechanisms whereby whole grains and legumes exert this effect. This is a comprehensive review that utilized all

literature examining the subsequent meal effect found using the following search strategy: whole grain plus fermentation or glycemia or insulinemia or (meal and lunch) or (meal and dinner) or (breakfast and lunch) or (dinner and breakfast). If a paper was found that studied any form of whole grain and glycemia at a subsequent meal, it was included. No studies that met this criterion were excluded for any reason.

2. Discussion

2.1. Subsequent Meal Effect. The subsequent meal effect (or second meal effect) describes the ability of whole grain and legume intake at a single meal to influence postprandial glycemia at the next meal. That is, inclusion of whole grains or legumes at breakfast decreases postprandial glycemia at both lunch and dinner on the same day whereas consumption of a whole grain or lentil dinner reduces glycemia at breakfast the following morning (Table 1). The subsequent meal is always provided as a standardized food or meal with no difference in energy, macronutrient content, or total fiber such that any difference in glycemia following this meal can be attributed to the composition of the first or initial meal.

Barley kernels, rye kernels, and legumes, whether consumed as part of a dinner or breakfast, reduce postprandial glycemia at a subsequent meal (Table 1). Oats and wholemeal bread, which contains processed whole grain material, do not provide a subsequent meal effect (Table 1). Indeed, processing, milling, and cooking at high temperatures may negate the subsequent meal effect or, in some instances, can even exacerbate postprandial glycemia at a subsequent meal. In a study utilizing barley breads cooked under different conditions, only breads containing barley prepared in pumpernickel style, cooked at low temperatures over a long period of time, decreased glycemia at a subsequent meal compared with white wheat bread (WWB) [10]. Bread containing an equivalent amount of barley but cooked under standard bread-baking conditions had no effect on glycemia at a subsequent meal. When barley kernels are milled and cooked in a microwave as porridge, glycemia at the next meal is greater than that observed using WWB as the first meal [11]. Therefore, it is important to consider not only the type of whole grain consumed but also the form of the grain at the time of consumption. Many commercial whole grain products contain highly milled whole grains which have been cooked or extruded to form the final product. Some of these products, such as pasta, result in a structural matrix that decreases postprandial glycemia relative to bread [12]. However, it is possible that some of these milled/cooked foods may not exert a subsequent meal effect on glycemia; so, should initial glycemia play a role in the subsequent meal effect, it seems prudent to advise consumption of whole grains in their native form when possible to elicit the full benefit from their consumption.

All but one study [13] conducted to examine the subsequent meal effect have standardized carbohydrate intake at the first meal by feeding equivalent amounts of available carbohydrate. Generally, 50 g of available carbohydrate was provided per test meal which is equivalent to the amount provided for glycemic index testing. Indeed, the primary goal of many studies was to investigate the subsequent meal effect of meals differing in glycemic index [10, 11, 14, 15, 17, 18]. However, the traditional method of calculation of available carbohydrate is fraught with difficulty, especially in the case of whole grains and legumes which are high in insoluble fiber and resistant starch (RS) [19]. Conventional total fiber assays do not account for all of the RS present in a food such that simple subtraction of total fiber from total carbohydrate, the traditional way of calculating available carbohydrate, may overestimate available carbohydrate in high RS foods. One study did address this issue by assaying both the total fiber and RS content of meals and presenting meals with either 50 g available carbohydrate or 50 g available starch (taking RS into account) [15]. In this study, using barley kernels, adjustment for RS content did not affect the data in any way. However, the RS plus dietary fiber content of the two meals were the same so it is not surprising that there was no difference in effect. It still remains important to consider the method used to calculate available carbohydrate and ensure that calculations are accurate in order to interpret the resultant data.

A confounding factor of the studies conducted thus far is the use of single foods versus complete meals as the initial or first meal. The fat and protein quantity and quality are known to influence the rate of glucose absorption from a mixed meal [20, 21]. Therefore, the dynamics of immediate and subsequent meal glycemia are more complicated if the initial meal is a complete, mixed meal. It seems that serving a single food as the initial meal would simplify data interpretation except for the fact that, under free living conditions, people rarely, if ever, consume a single, stand-alone food as a meal or snack. Because the physiological properties of a food change in relation to other components present in a meal, it is important to examine the effects of whole grain and legume consumption as part of a complete meal. Barely 1/3 of studies conducted thus far utilize complete meals for the initial or first meal (Table 1). Although there is often good agreement between these studies and those utilizing single foods, Wolever et al. [14] showed that lentils fed as a single food decreased glucose area under the curve at a subsequent meal relative to WWB whereas lentils as part of a complete meal did not (Table 1). This data is further convoluted by the fact that the subsequent meals were different: for the lentils as a single food study, the subsequent meal was a drinkable glucose solution whereas the second meal for the lentils as part of a complete meal study was also a complete, mixed meal. Therefore, the form of the subsequent meal could also have influenced the difference in response to lentils in this series of experiments. Clearly, for optimal relevance to the free-living condition and for clarity of data comparison, the initial meal should contain whole grains or legumes as part of a mixed, complete meal and, ideally, the subsequent meal would also be a complete, mixed meal. Further studies are necessary to standardize the optimal conditions for assessing the subsequent meal effect.

2.2. Implications for Blood Glucose Control. The subsequent meal effect has important implications for the day-long

Table 1: Subsequent meal effect of whole grains and lentils.

Study	Initial/ 1st meal	Subsequent meal	Time between meals (h)	Control food[#]	Test food	Complete meal (Y/N)	Effect of test food on glucose at subsequent meal	Breath hydrogen (fermentation)
Jenkins et al.* [13]	B/F	Lunch	4	WWB	Lentils	Y	↓ AUC by 38%	↑ 200%
Wolever et al. [14]								
(1)	Dinner	B/F	?	Glucose	Lentils	N	↓ AUC	N/A
(2)	Dinner	B/F	?	WWB	Whole meal bread	N	=	
(3)	Dinner	B/F	?	Bread and potato	Lentil and barley	Y	= AUC; ↓ mean postprandial [G]	
Liljeberg et al. [10]	B/F	Lunch	4	WWB	Barley bread (long, slow cooking) + BF	Y	↓ only with added BF, not barley bread alone	N/A
Granfeldt et al. [15]	Dinner	B/F	?	WWB	Barley kernels	N	↓ AUC	N/A
Samra and Anderson [16]	B/F	Lunch[†]	1.25	WWB/ Cornflakes	Fiber One cereal	Y	↓ AUC	
Nilsson et al. [17]	Dinner	B/F	10.5	WWB	Barley kernels orcut barley	N	↓ AUC by 28% ↓ peak [G]	↑
Nilsson et al. [18]	Dinner	B/F	10.5	WWB/ Spaghetti	Spaghetti + high-dose BF	N	↓ AUC	↑
Nilsson et al. [11]	B/F	Lunch	4	WWB	Rye kernels	N	↓ AUC	↑
					Oat		= AUC	=
					Barley kernels		↓ AUC	↑
		Dinner	10.5	WWB	Rye kernels	N	↓ AUC	=
					Oat		= AUC	↑
					Barley kernels		↓ AUC	↑

B/F: breakfast; AUC: area under the curve; WWB; white wheat bread; BF: barley fiber; [G]: glucose concentration.
All meals matched for available CHO except for*.
[#]Control foods were not prepared with whole grains.
[†]The timing of the subsequent meal (1.25 h after BF) is too short for the second meal to be considered "lunch".

control of blood glucose and, ultimately, long-term glucose tolerance. The day-long effect of whole grain and legume consumption [11] may be more important to health outcomes than the acute effect at a single meal per se as postprandial hyperglycemia and hyperinsulinemia have been implicated in the development of insulin resistance in both humans and rats. In humans, large postprandial glycemia rises are associated with an increased concentration of free fatty acids in the plasma [22, 23] which causes a decrease in glucose oxidation [22], presumably via the glucose-fatty acid cycle [24], and, ultimately, impairment of insulin sensitivity [25]. Postprandial hyperinsulinemia has also been shown to decrease glucose uptake in muscles and increase glucose uptake in adipose tissue through a change in GLUT 4 mRNA and protein abundance [26, 27] and causes down-regulation of insulin receptors in humans [28]. Thus, attenuation of postprandial glycemia over the course of the day would be expected to have important long-term health implications in healthy adults, particularly with regard to diabetes prevention.

It is important to note that all studies investigating the subsequent meal effect with whole grains and legumes have used healthy adults as study subjects without exception. In these subjects, glucose tolerance decreased throughout the day [11] which is in contrast to diabetics in whom glucose tolerance increases between morning and evening. Furthermore, diabetic individuals could most benefit from both acute and day-long suppression of glucose peaks as well as the lower rate of increase and decrease in plasma glucose concentrations observed in studies with healthy adults. Therefore, it is important to examine whether the subsequent meal effect of whole grain or legume consumption is apparent in diabetics who are characterized by frank insulin resistance. Although no such studies have been undertaken, a study which examined the effect of meal size on the subsequent meal effect in type 1 diabetic subjects discovered that postprandial glycemia at dinner was higher following a large lunch (50% of daily caloric needs) than a small lunch (25% of daily caloric needs). So, it is reasonable to suspect that the subsequent meal effect of whole grains and legumes may also elicit a measurable effect in diabetic subjects.

If the subsequent meal effect is evident in diabetic individuals, it will be important to determine how this affects insulin dosing throughout the day. It may be necessary to

develop an algorithm for the "carb counting" or exchange systems that are commonly employed to estimate insulin doses that incorporates a factor for whole grain or legume consumption at previous meals. Additionally, it may be possible to include whole grains and/or legumes as part of a meal that would normally elicit higher blood glucose concentrations to prevent rises in HbA1c levels. That is, by decreasing glycemia not only following the initial meal but also over the course of the day, the effect of ingesting rapidly absorbed carbohydrates on long-term glycemic control, as measured via HbA1c, may be diminished. Studies investigating this outcome need to be conducted.

It should be noted that while the subsequent meal effect may change insulin dosing requirements in diabetics, it may also be protective against hypoglycemia as the plasma glucose concentration following subsequent meals not only decreases the total glucose response (area under the curve) but also lowers the *rate of decrease* in plasma glucose concentration [14] even in the absence of a difference in glycemia following the initial meal [16]. Also, the plasma glucose concentration prior to the subsequent meal may be slightly higher following whole grain intake than WWB consumption [10, 11] which could prevent hypoglycemia.

2.3. Possible Mechanisms. There are many possible mechanisms whereby ingestion of whole grains or legumes could cause lowering of glycemia at a subsequent meal. Some likely candidates are (1) the effect of immediate reductions in glycemia (following the initial meal) on subsequent glucose metabolism/tolerance and, (2) fermentation of indigestible carbohydrate.

Insoluble fiber present in legumes and whole grains may exert effects on lowering digestion and the rate of absorption of carbohydrates, with consequent lowering of postprandial glycemia, but does not seem to be linked with the subsequent meal effect. In a study which added barley fiber at the same levels found in whole barley kernels to WWB or spaghetti, there was no subsequent meal effect versus WWB [18]. A subsequent meal effect was only observed when twice the amount of barley fiber found in whole barley kernels was added to WWB. Additionally, when whole grain barley was milled into flour and served as porridge, there was a detrimental effect on subsequent meal glycemia despite the presence of the same amount of insoluble and total fiber as in the intact barley kernel which significantly lowered subsequent meal glycemia [11]. Thus, it is unlikely that insoluble fiber *per se* plays a significant role in the mechanism responsible for the subsequent meal effect.

2.3.1. Immediate Reductions in Glycemia Following the Initial Meal. In many cases, postprandial glycemia following the initial meal, or immediate glycemia, is lowered by whole grain and legume intake and influences subsequent meal glycemia (e.g., [10, 11, 14]). In these studies there is a direct correlation between the reduction in immediate glycemia and the magnitude of the second meal effect. So, under these conditions, immediate glycemia seems to play a role in facilitating the second meal effect. It has been hypothesized that lower postprandial glycemia decreases oxidative stress by attenuating cytokine production in healthy adults [11] which has been shown to impair insulin signaling [29]. The effect of glycemia on circulating free fatty acid concentrations, which are associated with impaired insulin action and, therefore, lower glucose sensitivity [30], may also contribute to the subsequent meal effect. In one study, whole grain consumption at dinner significantly decreased fasting free fatty acid concentrations [17] whereas another found that, in response to a lentil dinner, there was no difference in fasting free fatty acid concentrations the following morning yet still there was a second meal effect [14]. Evidently, this is a possible mechanism of action but there is a paucity of data to support this theory, and further studies need to be conducted to determine how significant this mechanism might be in eliciting the subsequent meal effect.

It is reported in the literature that immediate glycemia is an important mechanism for the second meal effect when the test meal is breakfast and the subsequent meal is lunch. That is, when the two meals are only several hours apart. However, in studies where subsequent meal glycemia is closely linked with initial meal glycemia, two are breakfast-lunch studies [10, 11] whereas one is a dinner-breakfast study with a much longer time between the test meals [14]. Additionally, in the overnight condition, the subsequent meal effect can occur in the absence of any immediate change in glycemia following the initial meal and the subsequent meal effect under these conditions may stem from carbohydrate fermentation in the large bowel.

A decrease in immediate glycemia following the initial meal is not obligatory for the subsequent meal effect to occur, even in a breakfast-lunch paradigm [16] and, conversely, a decrease following an initial breakfast meal does not equate to a reduction in glycemia at the subsequent meal [13]. In this study [13], a lentil breakfast significantly reduced postprandial glycemia following a standard lunch but WWB nibbled over time to mimic the glycemia observed upon lentil ingestion did not result in a subsequent meal effect. Thus, although there are plausible mechanisms by which reduced immediate glycemia could contribute to both the subsequent meal effect and the reduction in diabetes and cardiovascular disease incidence observed with high whole grain intake, the direct evidence for immediate glycemia as a mechanism for the subsequent meal effect is, at best, equivocal.

2.3.2. Fermentation of Indigestible Carbohydrates. Fermentation of indigestible carbohydrates produces SCFA which have been associated with improved insulin sensitivity and glucose tolerance due to decreased hepatic glucose output and free fatty acid concentrations [31]. In studies examining the role of whole grain and legume consumption on the subsequent meal effect, those that measure fermentation find a strong association between fermentation and reduced glycemia at a subsequent meal. In fact, in all cases, a reduction in glycemia at a subsequent meal is associated with a significant increase in carbohydrate fermentation when measured (Table 1). Also, although fermentation has been rejected as a mechanism for the subsequent meal

effect in breakfast-lunch studies with a protracted timeframe, there have been reports of measurable fermentation at the lunch meal, particularly in the case of rye kernel ingestion at breakfast [11]. In a more thorough investigation of this concept, it was found that significant concentrations of acetate appear in the blood within 4 hours of barley kernel ingestion whereas butyrate and propionate appear later (6–15 h after ingestion) [32]. Thus, it is likely that the acetate fraction of SCFA could be partly responsible for the subsequent meal effect in breakfast-lunch studies whereas butyrate and propionate may be more important for modulating carbohydrate tolerance over a longer time frame in dinner-breakfast studies.

In support of fermentation as the most significant contributor to the subsequent meal effect are numerous studies finding that the different particle sizes and composition of whole grains produce different amounts of SCFA with smaller, processed samples not causing an increase in butyrate concentrations [33]. These data are consistent with the finding that intact whole grains elicit the strongest subsequent meal effect which is lost upon extensive milling. It is important to note that, in mixed meal studies, other food components such as protein can modulate or facilitate fermentation and the interaction between food components may also, therefore, contribute to the subsequent meal effect through their effects on fermentation.

A single study has directly investigated the effect of fermentation on subsequent meal glycemia [34]. The test meals in this study contained either nonfermentable amylopectin plus cellulose, amylopectin plus fermentable lactulose, or fermentable amylose plus cellulose. Meals containing these ingredients were presented at breakfast with subsequent meal glycemia measured following a standardized lunch meal five hours later. Both of the meals containing fermentable carbohydrate decreased subsequent meal glycemia relative to the amylopectin meal [34]. The amylose meal also decreased immediate glycemia and insulinemia (following the first meal, breakfast) whereas the lactulose meal did not. The lactulose meal, however, caused a significant increase in nonesterified fatty acid concentrations and gastric emptying time following the initial meal which the amylose meal did not [34]. Therefore, the mechanism for the subsequent meal effect involved fermentation and decreased initial glycemia/insulinemia for the amylose meal whereas fermentation plus changes in gastric emptying rate and nonesterified fatty acid concentrations seem to cause this effect for the lactulose meal. Thus, it seems that many factors may be involved in eliciting the subsequent meal effect with fermentation of indigestible carbohydrate acting as a common, key modulator.

2.4. The Resistant Starch Caveat. RS has the intrinsic properties of both soluble and insoluble fiber. As such, it can decrease transit time through the gut and increase stool bulk but is also an excellent substrate for fermentation in the large bowel which decreases bowel pH and generates short chain fatty acids (SCFA). RS is known to decrease plasma glycemia and insulinemia following ingestion [35]. Therefore, the RS content of whole grains and legumes may facilitate the second meal effect, primarily through fermentation in the bowel or due its effect on postprandial glycemia and insulinemia. Likely, both mechanisms are involved during RS consumption. Test meals high in RS have elicited a strong subsequent meal effect both during a breakfast-lunch paradigm, where postprandial may play a role in facilitating this effect [11], and a dinner-breakfast model, in which fermentation seems to be the predominate driving factor [18]. Although there is scant evidence to support the role of immediate postprandial glycemia reduction as a mechanism for the subsequent meal effect, breakfast-lunch studies where the time between meals is 4 h, are probably too short to assess the effects of RS fermentation which starts at about 6–8 h following ingestion in healthy adults [36]. Therefore, factors beyond fermentation may play a role in eliciting the subsequent meal effect in response to high RS foods.

Most studies examining the subsequent meal effect of whole grain or legume intake do not independently report the RS content of the test meals. Rather, a combined RS plus dietary fiber number is provided. In those studies that do report RS as a discrete variable in the diet [10, 11, 18], only one has adequate controls to determine if RS exerts any independent effect beyond total fiber or RS + total fiber [11]. By comparing the data in this study from barley kernels (8 g RS, 9.1 g, total fiber, 17.1 g RS + total fiber), rye kernels (matched to barley for RS + total fiber but lower in RS; 3.7 g RS, 14.2 g total fiber, 17.9 g RS + total fiber), and barley porridge (matched to barley for total fiber but low in RS; 1.7 g RS, 9.2 g total fiber, 10.9 g RS + total fiber), it can be seen that the RS content of whole grains may be an independent contributor to the subsequent meal effect. Only the barley kernel breakfast significantly increased prelunch basal glucose concentration relative to WWB and, while both barley and rye kernel meals decreased total day-long glucose area under the curve, barley kernels had a larger effect. Finally, barley porridge which is low in RS but matched to barley kernels for total fiber produced no subsequent meal effect [11], indicating that RS exerts an effect beyond that of fiber.

3. Conclusions

The ingestion of whole grains and legumes may cause diminution of postprandial glycemia not only at the meal in which they were consumed but also at subsequent meals. This effect is apparent whether whole grains and legumes are consumed during breakfast, causing decreased glycemia for the remainder of the day, or at dinner, causing lower glycemia at breakfast the following morning. This effect may prove useful in public health efforts for diabetes prevention and could be a factor in the documented relationship between whole grain intake and lower risk of diabetes. Additionally, by decreasing glycemia not only following the initial meal but also over the course of the day, the effect of ingesting rapidly absorbed carbohydrates on long-term glycemic control, as measured via HbA1c, may be diminished if whole grains or legumes are also consumed. This is a hypothesis that warrants further investigation. It is important to note that extensive milling or cooking negates the subsequent meal

effect so whole grains and legumes should be consumed in their native state or with minimal processing for full benefit. Finally, it may be concluded that fermentation of indigestible carbohydrate is the primary mechanism whereby whole grains and legumes exert the subsequent meal effect.

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