Effects of whole and refined grains in a weight-loss diet on markers of metabolic syndrome in individuals with increased waist circumference: a randomized controlled-feeding trial\textsuperscript{1–3}

Jessica A Grieger, Susan K Lemieux, and Penny M Kris-Etherton

ABSTRACT

Background: Higher whole-grain (WG) intake is associated with a lower prevalence of metabolic syndrome (MetS); however, there is inconsistent clinical evidence with regard to the benefit of WGs compared with refined grains (RGs) on MetS.

Objective: We hypothesized that consuming WGs in the place of RGs would improve MetS criteria in individuals with or at risk of MetS.

Design: A randomized, controlled, open-label parallel study was conducted in 50 overweight and obese individuals with increased waist circumference and one or more other MetS criteria. Participants consumed a controlled weight-loss diet containing either WG or RG (control) products for 12 wk. Body composition, MetS criteria and related markers, and plasma alkylresorcinols (compliance marker of WG intake) were measured at baseline and at 6 and 12 wk. A subgroup \((n=28)\) underwent magnetic resonance imaging to quantify subcutaneous and visceral adipose tissue (AT).

Results: Baseline variables were not significantly different between treatment groups; however, the RG group tended to have higher triglycerides and lower high-density lipoprotein (HDL) cholesterol \((P=0.06)\). Alkylresorcinols increased with consumption of the WG diet and did not change with consumption of the RG diet \((\text{time} \times \text{treatment}, P<0.0001)\), which showed dietary compliance. There were no differences in anthropometric changes between groups; however, weight, body mass index, and percentage of body AT decreased at both 6 and 12 wk \((P<0.05)\), and reductions in percentage of abdominal AT occurred by 6 wk and did not change between 6 and 12 wk \((P=0.09)\). Both glucose \((P=0.02)\) and HDL cholesterol \((P=0.04)\) were lower with the consumption of the WG compared with the RG diet. However, when noncompliant individuals \((n=3)\) were removed, the glucose effect was stronger \((P=0.01)\) and the HDL-cholesterol effect was no longer significant \((P=0.14)\).

Conclusions: Replacing RGs with WGs within a weight-loss diet does not benefitably affect abdominal AT loss and has modest effects on markers of MetS. WGs appear to be effective at normalizing blood glucose concentrations, especially in those individuals with prediabetes. This trial was registered at www.clinicaltrials.gov as NCT00924521.

INTRODUCTION

One-third of US adults have diagnosed metabolic syndrome (MetS)\textsuperscript{4}, 90\% of whom are overweight or obese (1). MetS is a composite of risk factors associated with increased risk of type 2 diabetes and cardiovascular disease (CVD) (2). The criteria for MetS include having \(\geq3\) of the following clinical indicators: increased waist circumference, fasting glucose, triglycerides, and blood pressure (BP) and decreased HDL cholesterol (2). Excess abdominal adipose tissue (AT) and accompanying insulin resistance are believed to be the underlying causes of MetS (3).

Nutritional approaches to achieve ideal body weight are important for the prevention of obesity-related diseases. In addition to weight loss, dietary advice often includes replacing refined-grain (RG) with whole-grain (WG) foods (4). WGs contain fibrous bran, starchy endosperm, and nutrient-rich germ. Removing the bran and germ, or “refining” the grain, reduces the fiber, vitamin, mineral, and phytochemical contents of the grain product (4).

Epidemiologic research consistently links increased WG consumption to lower incidence of metabolic diseases [ie, MetS (5), type 2 diabetes (6), and CVD (7)] and reduced abdominal fat mass.

\footnotesize{\textsuperscript{1}From the Departments of Nutritional Sciences (KHJ, SGW, AMH, JAG, and PMK-E), Biobehavioral Health (SGW), and Veterinary and Biomedical Science (JPVH); the Center of Excellence in Nutrigenomics (JPVH and PMK-E); and the Social, Life, and Engineering Sciences Imaging Center (SKL), Pennsylvania State University, University Park, PA; the Bell Institute of Health and Nutrition, General Mills Inc, Minneapolis, MN (SSJ); the Nestlé Research Center, Lausanne, Switzerland (ABR); the Chalmers University of Technology, Gothenburg, Sweden (ABR); the Nutritional Physiology Research Centre, University of South Australia, Adelaide, Australia (AMH); and the Robinson Institute, Adelaide University, Adelaide, Australia (JAG).

\footnotesize{\textsuperscript{2}Supported by grants from the Bell Institute of Health and Nutrition (General Mills, Inc) and NIH grant M01RR10732. KHJ was supported by the Nestlé PhD, RD Training Fellowship, which is a competitive award funded by Nestlé Research Center for a nutritional science graduate student pursuing both degrees at the Pennsylvania State University. Alkylresorcinol analysis was funded by Cereal Partners Worldwide, a joint venture between General Mills, Inc, and Nestlé SA to produce and sell breakfast cereals outside of the United States and Canada.

\footnotesize{\textsuperscript{3}Address reprint requests and correspondence to PM Kris-Etherton, 110 Chandlee Laboratory, University Park, PA 16802. E-mail: pmk3@psu.edu.

\footnotesize{\textsuperscript{4}Abbreviations used: AT, adipose tissue; BP, blood pressure; CRC, clinical research center; CRP, C-reactive protein; CVD, cardiovascular disease; DXA, dual-energy X-ray absorptiometry; L3, third lumbar vertebra; MetS, metabolic syndrome; RG, refined grain; TC, total cholesterol; WG, whole grain.

Received October 31, 2013. Accepted for publication May 8, 2014. First published online June 18, 2014; doi: 10.3945/ajcn.113.078048.}
adiposity [estimated by waist circumference (8) and percentage of abdominal (9) and visceral (10) AT]. Although this literature is consistently positive for WGs, the magnitude of effect is often small. For example, every 40 g WGs consumed per day was related to a reduction in weight gain of 0.49 kg over 10 y (11). A recent meta-analysis of randomized controlled trials comparing WGs and RGs showed that WGs may accelerate body AT loss (although not weight loss) (12). Moreover, replacing RGs with WGs during weight loss for 12 wk caused a greater decrease in percentage of abdominal AT in a clinical trial in free-living individuals with MetS (13), but this was not shown in a similar study (14). The consumption of WGs may reduce the risk of MetS via preferential reduction in abdominal AT during weight loss.

Clinical studies evaluating the effects of WGs on MetS characteristics have yielded mixed findings, with beneficial effects being reported for different MetS components in each study (13–16). This discrepancy between epidemiologic and clinical studies has been attributed, in part, to inconsistent adherence in free-living studies and the variety, type, and form in which the grain was consumed (13, 15). To control this variability, we first used a controlled-feeding study design and assessed a biomarker of WG wheat intake, plasma alkylresorcinols (17), to improve participant adherence. Second, the diets differed only in the type of grain products used (WGs or RGs). Third, we designed diets with grain products that were composed primarily of wheat, which make up a majority of the US WG intake. We hypothesized that the WG diet would improve MetS criteria, particularly abdominal obesity, more than the RG diet in overweight and obese participants with increased waist circumference. Primary endpoints were percentage of abdominal fat and MetS characteristics, and secondary endpoints included insulin, total and LDL cholesterol, inflammatory markers, adipokines, and other measurements of body composition.

SUBJECTS AND METHODS

Subjects

Eligible participants were overweight or obese [BMI (in kg/m²) 25–42], 35–55 y of age, and were required to have a waist circumference ≥102 cm (men) or ≥88 cm (women) and at least one other criterion of MetS (18), as follows: fasting plasma glucose ≥100 mg/dL, fasting serum triglycerides ≥150 mg/dL, BP ≥130/≥85 mm Hg, and/or fasting serum HDL cholesterol <50 mg/dL (women) or <40 mg/dL (men). Exclusion criteria included use of medications affecting glucose or lipid metabolism, frequent (>4 times/wk) use of anti-inflammatory medications, pregnancy or lactation, smoking, high alcohol intake (>14 drinks/wk), and diagnosed CVD, diabetes, or inflammatory disease. Two alcoholic drinks per week were allowed for participants during the study, but alcohol was restricted for 48 h before any clinic visits. BP medications were allowed (n = 2); however, participants taking BP medications still needed to have at least 2 other markers of MetS to qualify for the study. Participants provided informed consent before any clinical procedures were performed at the screening appointment. This study was conducted according to the guidelines of Helsinki, and the Institutional Review Board at the Pennsylvania State University approved all procedures involving human participants. The trial was registered at clinicaltrials.gov (identifier: NCT00924521).

Study design and intervention

This was a 12-wk, randomized, parallel-arm, open-label controlled-feeding trial comparing the effects of WGs with RGs (control) on markers of MetS. Participants were screened at the clinical research center (CRC) on the Pennsylvania State University campus within 6 mo before starting the study to determine eligibility. Eligible individuals (n = 60) were randomly assigned to either the WG or RG diet group for the entire 12 wk by using a computer-generated random-number assignment. Participants could not be blinded to their group assignment. An unblinded study coordinator stratified participants by age, sex, and BMI and conducted all data analyses. Outcome assessors (ie, nurses and technicians) were blinded. Diets were tailored to individual energy requirements by using the Harris-Benedict equation with a low activity factor of 1.3 (19). Energy levels ranged from 1600 to 3600 kcal/d; the WG diets contained between 163 and 301 g WGs/d, and the RG diets contained 0 g WGs/d (Table 1). All participants were placed on (what was intended to be) an isocaloric, weight-maintenance diet for the first 6 wk, followed by a hypocaloric diet (~500 kcal energy deficit/d) for the second 6 wk. Average caloric intake during the isocaloric phase was 3200 kcal/d (range: 2700–3900 kcal/d) for men and 2350 kcal/d (range: 2100–3500 kcal/d) for women. During the hypocaloric period, average intake was 2500 kcal/d (range: 1600–3400 kcal/d) for men and 1750 kcal/d (range: 1600–2800 kcal/d) for women. During the second phase, the meals were composed of the same foods but were proportionally smaller, with the exception of some prepackaged foods (chip bags, granola bars). Significant weight loss occurred on both calorie levels in both the WG and RG groups; therefore, the isocaloric and hypocaloric phases were pooled to compare the difference between WGs and RGs after 12 wk of weight loss on controlled diets. To enhance compliance, participants were given the option to take a 1- to 2-wk break after the first 6-wk diet period. Nineteen (WG group: n = 7; RG group: n = 12) of 50 participants who completed the study chose to take the break; the remainder transitioned to the next phase of the study immediately. There was no difference in total weight lost between those who took the compliance break.

### TABLE 1

<table>
<thead>
<tr>
<th>Energy level</th>
<th>Servings of WGs</th>
<th>Amount of WGs</th>
<th>Average dietary alkylresorcinols</th>
</tr>
</thead>
<tbody>
<tr>
<td>1600 kcal</td>
<td>5.8</td>
<td>163</td>
<td>—</td>
</tr>
<tr>
<td>1800 kcal</td>
<td>5.9</td>
<td>164</td>
<td>56.3 ± 8.2</td>
</tr>
<tr>
<td>2100 kcal</td>
<td>6.7</td>
<td>187</td>
<td>65.7 ± 9.6</td>
</tr>
<tr>
<td>2400 kcal</td>
<td>7.8</td>
<td>213</td>
<td>75.1 ± 11.0</td>
</tr>
<tr>
<td>2700 kcal</td>
<td>8.7</td>
<td>228</td>
<td>84.5 ± 12.3</td>
</tr>
<tr>
<td>3000 kcal</td>
<td>9.7</td>
<td>258</td>
<td>93.9 ± 13.7</td>
</tr>
<tr>
<td>3300 kcal</td>
<td>10.5</td>
<td>280</td>
<td>103.3 ± 15.1</td>
</tr>
<tr>
<td>3600 kcal</td>
<td>11.5</td>
<td>301</td>
<td>112.7 ± 16.4</td>
</tr>
</tbody>
</table>

1. WG, whole grain.
2. Values are kcal/d.
3. Estimated alkylresorcinol amounts for each calorie level were based on alkylresorcinol amounts measured in grain products and the amount of grain consumed for that calorie level; the average of 6 daily menus was calculated. Values are means ± SDs.
4. Alkylresorcinol amounts for the 1600-kcal menu were not calculated because WG amounts were very similar to the 1800-kcal amount.
and those who did not [break (−4.1 ± 0.5 kg) compared with no break (−5.0 ± 0.4 kg); \( P = 0.2 \)]. Participants completed a variety of clinical assessments over 2 consecutive days before the intervention and after 6 and 12 wk of consuming the diets. The first participants began the study in March 2009, and the final participants completed the study by May 2011.

The WG and RG diets used the same 6-d cycle menus with the exception of the grain products. Participants assigned to the WG diet consumed all WG products from a variety of grain types, whereas those receiving the RG diet consumed the RG counterpart. An example of the grain product substitutions in a sample 1-d menu is shown in Supplemental Table 1 under “Supplemental data” in the online issue. The American Association of Cereal Chemists and the Food and Drug Administration define WG as “the intact, ground, cracked, or flaked caryopsis, whose principal anatomical components—the starchy endosperm, germ and bran—are present in the same relative proportions as they exist in the intact caryopsis” (20). WG products made from milled flour (eg, bread, pasta) were required to have >51% of dry weight from WG flour. When possible, WG products carrying the 100% Whole Grain stamp were selected, which indicated that each grain serving contained at least 16 g WG and used 100% WG flour. The WG and alkylresorcinol contents of the WG products in the study are described in Supplemental Table 2 under “Supplemental data” in the online issue. The top 3 grains represented 77% and 63% of the grains consumed with the WG and RG diets, respectively.

Both diets had the same macronutrient composition and were designed to meet National Cholesterol Education Program guidelines (18) for saturated fat (<7% total energy), monounsaturated fats (~10% and ~7% total energy, respectively), total cholesterol (<200 mg/d), and total fiber (>20 g/d) (Table 2). The low-fat diet was selected as a safe, healthy background diet that would be appropriate in both weight-maintenance and weight-loss settings. All meals and snacks were prepared at 1 of 2 metabolic kitchens on the university campus. Participants were required to come to either of the metabolic kitchens on Monday through Friday to pick up and/or eat their meals (weekend meals were packed and provided on Friday), fill out compliance forms, and record their weight (self-report).

### Clinical assessments

Body weight was measured with subjects wearing light clothing and no shoes every 3 wk at the CRC after a 12-h overnight fast. Only body weights recorded at the CRC were used for statistical comparisons. Blood was drawn in the morning after a 12-h fast according to standardized protocol. Screening results were analyzed with the use of fresh blood by a clinical diagnostic testing center (Quest Diagnostics); serum and plasma aliquots in EDTA-coated tubes were stored at −80°C until time of analysis. Waist circumference was measured in accordance with the National Heart, Lung, and Blood Institute guidelines (21). BMI was calculated by using weight from each clinical visit and height measured at baseline. Percentage of abdominal AT was measured by using dual-energy X-ray absorptiometry (DXA) within a 50-cm² area around the center point of the midline between the lateral iliac crests and the lowest rib margins. Participants weighing <157 kg (n = 46) were measured with a hologic DXA (QDR-4500W; Hologic Corporation), and those ≥157 kg (n = 3) were measured with a GE Lunar iDXA (General Electric). The abdominal region of interest could only be measured with hologic DXA; therefore, 3 individuals receiving the WG (n = 2) and RG (n = 1) diets could not be analyzed for the primary endpoint. Percentage of AT was used as the primary body composition endpoint to minimize variability in output by the 2 DXA scanners. BP was measured by trained nurses with the use of a standing mercury manometer (Baumanometer). Participants sat for ≥5 min with their legs uncrossed before repeated measurements, which were taken ≥1 min apart; the average of 3 measurements was used.

Resting metabolic rate was measured at baseline and at the end of the study by using a Cosmed FitMate. The test was performed after participants fasted for 12 h, refrained from vigorous exercise for 24 h, and abstained from alcoholic and caffeinated beverages for 48 h. Participants rested for 30 min in a supine position shortly after arriving at the clinic. A mask connected to the Cosmed FitMate was then placed over their nose and mouth for 15 min to measure oxygen consumption and energy expenditure. A trained technician stayed with the participants during the test, noting changes in breath depth and frequency, fixing air leaks in the mask, and ensuring that participants were awake and comfortable.

### Biochemical analyses

Plasma glucose, total cholesterol, HDL cholesterol, and triglycerides from fasted samples taken on consecutive days were measured by using enzymatic procedures and spectrophotometry (Quest Diagnostics). LDL cholesterol was determined by using Friedewald’s equation: LDL cholesterol = total cholesterol (TC) – HDL cholesterol − (triglycerides ÷ 5) (18). Serum insulin and high-sensitivity C-reactive protein (CRP) were measured with an immunoassay technique and latex-enhanced immunonephelometry, respectively (Quest Diagnostics). CRP values >10 mg/L.
were not used for analysis, because this concentration indicates infection. HOMA-IR was calculated as follows: fasting glucose (mg/dL) × fasting insulin (mU/L)/405 (22). Serum total adiponectin, high-molecular-weight adiponectin, leptin, IL-6, and TNF-α were measured with ELISAs (R&D Systems) in duplicate (assay CVs <10%) according to the manufacturer’s protocols. Plasma alkylresorcinols were analyzed by using normal-phase liquid chromatography–tandem mass spectrometry (23) after extraction with diethyl ether. Intrabatch repeatability for each standard was <10%, and interbatch repeatability was <15%.

Subgroup: abdominal imaging scans

A subset (n = 28/60) of participants agreed to undergo abdominal MRI scans to assess changes in subcutaneous and visceral AT. MRI data were acquired with a Siemens Magnetom Trio 3.0 Tesla scanner. Single-slice axial abdominal fast spin echo images were acquired (repetition time/echo time = 100/2.46 ms; flip angle = 70°; number of excitations =1; bandwidth = 280 kHz; matrix = 256 × 192; slice thickness = 8 mm; echo train length = 4) by using a Siemens Magnetom Trio body coil. Three consecutive slices surrounding the third lumbar vertebra (L3) were analyzed for subcutaneous and visceral AT volume by using a program developed in-house (Matlab; MathWorks). Two trained technicians manually traced all slices, and the average of the 2 was used. The sum of 3 slices surrounding L3 was chosen because excess AT in this area of the abdomen has been shown to have the highest correlation with metabolic dysfunction (24, 25).

Statistical methods

All statistical analyses were performed on SAS software (version 9.2; SAS Institute). Nonparametric r-tests (PROC NPAR1WAY) and chi-square tests were used to assess baseline differences in continuous and categorical variables, respectively. For biochemical variables measured on 2 consecutive days, an average was used. Linear-mixed models (PROC MIXED) were used to analyze both raw values and change score models. Log-transformed alkylresorcinol values at 0, 6, and 12 wk were analyzed to assess compliance (time × treatment) and are presented as geometric means (95% CIs). Changes in body weight and composition were analyzed at 6 and 12 wk in models adjusted for age and sex. All other biomarkers were analyzed by comparing the total change over 12 wk between groups (WG compared with RG) in unadjusted and adjusted models. The first adjusted model included age, sex, and baseline BMI; the second included these and weight loss. Reassessment without the “noncompliant” individuals (as determined by alkylresorcinol concentrations at 12 wk), interactions by sex (men compared with women), and compliance break status (those who took a 1–2 wk break after the first 6 wk of the diet compared with those who continued with the diet uninterrupted) were conducted for primary endpoints by using the model adjusted for age, sex, and baseline BMI. To determine the normality of the data, the skewness of the residuals from the models was assessed. Statistical outliers (± >3 SDs from mean or data points that skewed residuals) were removed as well as all CRP values >10 mg/L, which is indicative of infection. Geometric means (95% CIs) of baseline values and change scores ± SEMs from the unadjusted model are presented for the nonnormally distributed variables. Baseline means ± SDs and change scores ± SEMs are presented for variables with models having normally distributed residuals. Freeman-Halton adjustment of the Fisher’s exact test was used for the prediabetes subgroup analysis. Regression outputs (R², P value) between variables associated with alkylresorcinol changes are presented as exploratory analyses. Differences were considered significant at P < 0.05 and as tendencies at P < 0.10. P values for secondary outcomes were corrected for false discovery rate by using the Benjamini-Hochberg procedure.

The primary endpoint used to determine sample size was the change in percentage of abdominal AT over 12 wk. For 80% power to detect a difference of 1.75 ± 2.2% in percentage of abdominal AT loss between the 2 diet groups at an α level of 0.05, a final sample size of 50 participants was needed. Power calculations were based on data from a previous study in MetS participants consuming WG and RG diets (12). Per protocol analysis included only the data from participants who completed both phases of the study (n = 50). An uneven randomization was attributable to higher dropouts in the RG group. MetS criteria and percentage of abdominal AT were primary endpoints; secondary endpoints included lipoproteins, insulin, inflammatory markers, adipokines, and other measures of body composition.

RESULTS

Of the 438 respondents, 28% (n = 123) underwent clinical screening. 14% (n = 60) were randomly assigned, and 12% (n = 50) completed the study (Figure 1). Ten individuals discontinued participation in the study because of an inability to comply with the time commitment (n = 5), family emergency (n = 1), adverse reaction to the WG diet (n = 1), unrelated illness/injury

![Flow diagram of the study.](https://academic.oup.com/ajcn/article-abstract/100/2/577/4576509/flow_diagram.png)
Medication use

Diastolic BP (mm Hg) 25/25 85
Systolic BP (mm Hg) 25/25 125
Glucose (mg/dL) 6
Triglycerides (mg/dL) 78% (concentrations)
Waist circumference (cm) 25/25 112

Probable low–WG wheat or rye consumer (RG group), whereas the glucose and HDL-cholesterol effects (see Table 3) had an elevated TC:HDL-cholesterol ratio (P = 0.05; Table 5).

Participant compliance

Alkylresorcinol concentrations increased with the WG but not the RG diet over time (time × treatment, P < 0.0001; Figure 2). There was an ~6-fold increase during the first diet period (640% from baseline) in participants consumed more WGs compared with the second, lower-energy diet period (297% from baseline). Alkylresorcinol concentrations with the RG diet did not change. On the basis of dietary compliance records, the participants consumed all study foods and did not consume any nonstudy foods on 86% of reported days. Weekly physical activity records showed that participants maintained a stable activity level.

Weight and body composition

Reductions in body weight (RG group compared with WG group: −4.4 ± 0.4 compared with −5.0 ± 0.4 kg; total change from baseline, P < 0.001; Figure 3A), BMI (RG group compared with WG group: −1.5 ± 0.1 compared with −1.7 ± 0.1; P < 0.001), and percentage of body AT (RG group compared with WG group: −1.0 ± 0.2% compared with −0.8 ± 0.2%; P < 0.01) occurred in both diet groups during both the iso- and hypocaloric diet phases (time, P < 0.05). The reduction in percentage of abdominal AT at 6 wk was not significantly different from that at 12 wk (time, P = 0.09), indicating that most of the change in abdominal AT occurred during the first 6 wk in both groups (RG group compared with WG group: −1.2 ± 0.4% compared with −1.5 ± 0.4%; total change from baseline, P < 0.01; Figure 3B).

Metabolic syndrome

Group baseline values, change scores, and model effects for MetS criteria are shown in Table 4 (graphs in Supplemental
Triglyceride concentrations did not change over time in either of the men (men compared with women: P = 0.14). The interactions between treatment and sex or break interaction, but no

| TABLE 5 | Secondary outcomes: baseline values and total change scores in RG and WG groups† |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | RG/GW           | RG/GW           | RG/GW           | RG/GW           |
|                | Baseline†       | Δ12 wk†         | Baseline†       | Δ12 wk†         | Unadjusted     | Model 1       | Model 2       |
| Total adiponectin (ng/mL) | 25/25 | 7265 ± 4299 | −1019 ± 304      | 7685 ± 3998 | −1038 ± 304      | 0.97 | 0.96 | 0.96 |
| HMW adiponectin (ng/mL)‡ | 25/24 | 2372 (1768, 3181) | −577 ± 137      | 2518 (1941, 3268) | −175 ± 140      | 0.30 | 0.30 | 0.30 |
| Leptin (ng/mL)§ | 25/24 | 24 (18, 31) | −7.0 ± 1.6      | 23 (16, 31) | −10.1 ± 1.6      | 0.74 | 0.74 | 0.74 |
| TC:HDL ratio | 25/24 | 4.9 (4.4, 5.4) | −0.2 ± 0.1      | 4.4 (3.8, 5.0) | 0.2 ± 0.1      | 0.30 | 0.30 | 0.30 |
| LDL cholesterol (mg/dL) | 24/24 | 124 ± 31 | −12.8 ± 3.7      | 110 ± 36 | −11.6 ± 3.7      | 0.96 | 0.96 | 0.96 |
| CRP (mg/L)‡ | 25/17 | 2.1 (1.4, 3.1) | −0.6 ± 0.4      | 3.0 (2.0, 4.6) | −0.6 ± 0.5      | 0.96 | 0.96 | 0.96 |
| IL-6 (pg/mL)§ | 23/23 | 1.7 (1.4, 2.0) | 0.1 ± 0.2      | 1.8 (1.5, 2.2) | 0.3 ± 0.2      | 0.96 | 0.96 | 0.96 |
| TNF-α (pg/mL)§ | 24/24 | 1.4 (1.2, 1.7) | −0.1 ± 0.1      | 1.2 (1.0, 1.3) | 0 ± 0.1      | 0.74 | 0.74 | 0.74 |
| Insulin (uIU/mL)§ | 25/23 | 2.6 (1.7, 4.1) | −0.9 ± 0.7      | 3.4 (2.2, 5.4) | −0.7 ± 0.7      | 0.96 | 0.96 | 0.96 |
| HOMA-IR§ | 25/23 | 0.6 (0.4, 1.0) | −0.2 ± 0.2      | 0.8 (0.5, 1.3) | −0.2 ± 0.2      | 0.96 | 0.96 | 0.96 |
| RMR (kcal/d) | 24/24 | 1616 ± 415 | −148 ± 53      | 1626 ± 384 | −76 ± 52      | 0.74 | 0.74 | 0.74 |

† CRP, C-reactive protein; HMW, high-molecular-weight; RG, refined grain; RMR, resting metabolic rate; TC, total cholesterol; WG, whole grain.
‡ Unadjusted model compares the raw change over 12 wk between WG and RG groups; model 1 adjusted for age, sex, and baseline BMI; model 2 adjusted as in model 1 + weight loss (group difference, false discovery rate–adjusted P < 0.05).
§ Values are means ± SDs for normally distributed variables and geometric means (95% CIs) for nonnormally distributed variables.
† Values are change scores ± SEMs from the unadjusted model.
+ p < 0.05, change from baseline.
* Statistical outliers removed from change score analysis.
& Baseline group difference, P = 0.05; P values from nonparametric t test.
* CRP values >10 mg/L were removed because this concentration indicates infection.

Figure 1 under “Supplemental data” in the online issue). The reduction in glucose was greater with the WG diet than with the RG diet in unadjusted and adjusted models (P < 0.05). Removing noncompliant participants (n = 3) strengthened the effect (RG group compared with WG group: −0.9 ± 1.1 compared with −5.0 ± 1.2 mg/dL; P = 0.02). A treatment × break status interaction showed that those who took a break had a smaller reduction in glucose compared with those who did not (break compared with no break: −0.4 ± 1.3 kg compared with −4.0± 1.0 kg; break, P = 0.04), but this was not significantly different between groups (treatment × break, P = 0.75) and the effect of treatment was still significant (treatment, P = 0.01). There was no treatment × sex interaction for glucose. Of the individuals with prediabetes (fasting plasma glucose ≥100 mg/dL) at baseline, 90% (n = 9/10) from the WG group and 13% (n = 1/8) from the RG group had their prediabetes resolved after 12 wk (P = 0.04) (Figure 4). The change in alkylresorcinol was inversely related to the change in fasting blood glucose (R² = 0.25, P = 0.003).

HDL cholesterol decreased more in the WG group than in the RG group in unadjusted and adjusted models (P < 0.05). However, this effect was no longer significant after removing the noncompliant participants (RG group compared with WG group: −2.6 ± 0.8 compared with −4.3 ± 0.8 mg/dL; P = 0.14). The interactions between treatment and sex or break status were not significant for HDL cholesterol; however, women had a greater reduction in HDL cholesterol than did men (men compared with women: −2.0 ± 0.9 compared with −5.7 ± 0.9 mg/dL; sex, P < 0.01).

Waist circumference and systolic BP decreased in both groups after 12 wk (P < 0.05). Diastolic BP tended to decrease more in the RG group in unadjusted and adjusted models (P < 0.1). Triglyceride concentrations did not change over time in either of the groups. There was a treatment × break interaction, but no post hoc comparisons were significant (treatment × break, P = 0.04). None of the other markers of MetS correlated with changes in alkylresorcinol concentrations.

Secondary endpoints

LDL cholesterol, leptin, and total adiponectin decreased in both groups (P < 0.05; Table 5). There were no group differences for

FIGURE 2. Geometric mean (95% CI) alkylresorcinol concentrations at 0, 6, and 12 wk in participants consuming the whole- and refined-grain diets. Linear mixed models (PROC MIXED; SAS Institute) of log-transformed alkylresorcinol values at 0, 6, and 12 wk were used to determine differences between groups at different time points (time × treatment, P < 0.0001; post hoc differences are Tukey-adjusted). In the whole-grain group, alkylresorcinol values increased significantly from baseline compared with the refined-grain group at 6 and 12 wk. *Significant difference between groups at time point (P < 0.05). †Significant within-group difference from baseline (P < 0.05). ‡Significant within-group difference from 6 wk (P < 0.05).
Changes in high-molecular-weight adiponectin, TNF-α, and resting metabolic rate. No changes in fasting insulin, HOMA-IR, TC:HDL-cholesterol ratio, CRP, and IL-6 values were observed. Changes in secondary endpoints were not correlated with changes in alkylresorcinols.

**MRI subgroup**

Changes in both subcutaneous and visceral AT at the L3 level were not significantly different between groups after 12 wk (Table 6). Changes in AT depots were not correlated with changes in alkylresorcinols.

**DISCUSSION**

Both of the diets resulted in significant weight loss and elicited modest but generally beneficial effects on metabolic variables.

Although there were no differences between WG and RG groups over time for the primary endpoint, percentage of abdominal AT, there was a greater reduction in glucose with the WG diet compared with the RG diet. Moreover, the prevalence of prediabetes was markedly reduced with consumption of the WG diet (90%) compared with the RG diet (13%). HDL cholesterol decreased to a greater extent in participants consuming the WG diet, but this effect was no longer significant when removing potentially noncompliant subjects.

Post hoc analysis of data from the Diabetes Prevention Program (26) compared diabetes risk in individuals with prediabetes who achieved a normal fasting glucose concentration during 6 y in a lifestyle modification trial compared with participants with persistent hyperglycemia. Individuals whose glucose concentrations were normal (<100 mg/dL) at least once during the 6 annual visits were 56% less likely to develop type 2 diabetes compared with those whose glucose concentrations stayed in the prediabetic range. Although the magnitude of glucose reduction was modest with consumption of the WG diet, the resolution of prediabetes is a clinically significant finding.

In the WG literature, a variety of grains and endpoints have been the focus of previous randomized controlled trials, such as oats and LDL-cholesterol lowering (27), barley (28) or rye (29) and insulin sensitivity, and wheat and weight loss (13). In the United States, wheat products, especially ready-to-eat cereals and breads, comprise the majority of WGs that are consumed (30); therefore, results from studies using primarily wheat products are the most relevant to the US population. Clinical trials with similar study designs—parallel arm studies lasting 12–16 wk in overweight and obese individuals with the use of primarily wheat products (13–16, 29)—showed that WG diets improve AT loss and BP compared with RG diets with no effects on glucose or insulin. Our findings add to the literature that WGs have generally positive effects on MetS criteria.

Dietary adherence and exclusive consumption of WGs were integral design components of the present study. None of the aforementioned studies controlled the background diet, but 4 of the 5 provided the grain products to their participants (14–16, 29). Our participants consumed more WGs compared with other studies: 6–12 servings/d (~163–301 g WGs/d depending on the...
TABLE 6
Subcutaneous and visceral adipose tissue at the L3 level: baseline values and total change scores in the MRI subgroup

<table>
<thead>
<tr>
<th></th>
<th>RG/WG</th>
<th>Baseline</th>
<th>Δ12 wk</th>
<th>Group differences, $P^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous AT (g)</td>
<td>12/16</td>
<td>782 ± 242</td>
<td>−51 ± 27</td>
<td>0.06</td>
</tr>
<tr>
<td>Visceral AT (g)</td>
<td>12/16</td>
<td>571 ± 245</td>
<td>−51 ± 17</td>
<td>0.32</td>
</tr>
</tbody>
</table>

$^1$ n = 28. AT, adipose tissue; L3, third lumbar vertebra; RG, refined grain; WG, whole grain.

$^2$ Model 1 compares change in abdominal AT over 12 wk between WG and RG groups adjusted for age and sex; secondary outcomes, group difference

$P < 0.05$.

$^3$ Values are means ± SDs for normally distributed variables and geometric means (95% CIs) for nonnormally distributed variables.

$^4$ Values are change scores ± SEMs from the unadjusted model.

$^5$ $P < 0.05$, change from baseline.

HDL cholesterol decreased more with the WG diet than with the RG diet in unadjusted and partially adjusted models; however, the decrease in and subsequent maintenance of HDL-cholesterol concentrations were parallel between the WG and RG groups (Supplemental Figure 1 under “Supplemental data” in the online issue). Moreover, the removal of potentially noncompliant participants eliminated the effect. The larger reduction in HDL cholesterol with the WG diet may be attributable to a combination of higher baseline concentrations in the WG group and a low-fat, weight-loss background diet (40). Low-fat (and low-saturated-fat) diets typically lower LDL cholesterol, but HDL cholesterol is reduced as well (41). To this point, LDL cholesterol decreased by ~12% in both groups. The effect of WGs on HDL cholesterol must be interpreted with caution, and future research is warranted. Indeed, MetS-related dyslipidemia did not improve or worsen with WG feeding in related clinical trials (13–16, 29).

A study limitation is the heterogeneous study population (different MetS criteria, both sexes, and women in varying hormonal states); however, there was an equal distribution between the groups for hormonal status and sex, and conclusions can be generalized to a broader population. Another limitation was the inability to maintain the baseline weights of participants during the “isocaloric” phase of the study. Providing a low-energy-dense, isocaloric diet to overweight and obese individuals often will cause a weight fluctuation of 1–2 kg in the first phase; thus, incorporating a run-in period may have ameliorated this issue. Those who took the compliance break had less favorable changes that, in a different setting, subjects in the WG group may have prolonged meals or consumed smaller portions because of increased satiety.

HDL cholesterol decreased more with the WG diet than with the RG diet in unadjusted and partially adjusted models; however, the decrease in and subsequent maintenance of HDL-cholesterol concentrations were parallel between the WG and RG groups (Supplemental Figure 1 under “Supplemental data” in the online issue). Moreover, the removal of potentially noncompliant participants eliminated the effect. The larger reduction in HDL cholesterol with the WG diet may be attributable to a combination of higher baseline concentrations in the WG group and a low-fat, weight-loss background diet (40). Low-fat (and low-saturated-fat) diets typically lower LDL cholesterol, but HDL cholesterol is reduced as well (41). To this point, LDL cholesterol decreased by ~12% in both groups. The effect of WGs on HDL cholesterol must be interpreted with caution, and future research is warranted. Indeed, MetS-related dyslipidemia did not improve or worsen with WG feeding in related clinical trials (13–16, 29).

A study limitation is the heterogeneous study population (different MetS criteria, both sexes, and women in varying hormonal states); however, there was an equal distribution between the groups for hormonal status and sex, and conclusions can be generalized to a broader population. Another limitation was the inability to maintain the baseline weights of participants during the “isocaloric” phase of the study. Providing a low-energy-dense, isocaloric diet to overweight and obese individuals often will cause a weight fluctuation of 1–2 kg in the first phase; thus, incorporating a run-in period may have ameliorated this issue. Those who took the compliance break had less favorable changes that, in a different setting, subjects in the WG group may have prolonged meals or consumed smaller portions because of increased satiety.

HDL cholesterol decreased more with the WG diet than with the RG diet in unadjusted and partially adjusted models; however, the decrease in and subsequent maintenance of HDL-cholesterol concentrations were parallel between the WG and RG groups (Supplemental Figure 1 under “Supplemental data” in the online issue). Moreover, the removal of potentially noncompliant participants eliminated the effect. The larger reduction in HDL cholesterol with the WG diet may be attributable to a combination of higher baseline concentrations in the WG group and a low-fat, weight-loss background diet (40). Low-fat (and low-saturated-fat) diets typically lower LDL cholesterol, but HDL cholesterol is reduced as well (41). To this point, LDL cholesterol decreased by ~12% in both groups. The effect of WGs on HDL cholesterol must be interpreted with caution, and future research is warranted. Indeed, MetS-related dyslipidemia did not improve or worsen with WG feeding in related clinical trials (13–16, 29).

A study limitation is the heterogeneous study population (different MetS criteria, both sexes, and women in varying hormonal states); however, there was an equal distribution between the groups for hormonal status and sex, and conclusions can be generalized to a broader population. Another limitation was the inability to maintain the baseline weights of participants during the “isocaloric” phase of the study. Providing a low-energy-dense, isocaloric diet to overweight and obese individuals often will cause a weight fluctuation of 1–2 kg in the first phase; thus, incorporating a run-in period may have ameliorated this issue. Those who took the compliance break had less favorable changes that, in a different setting, subjects in the WG group may have prolonged meals or consumed smaller portions because of increased satiety.

HDL cholesterol decreased more with the WG diet than with the RG diet in unadjusted and partially adjusted models; however, the decrease in and subsequent maintenance of HDL-cholesterol concentrations were parallel between the WG and RG groups (Supplemental Figure 1 under “Supplemental data” in the online issue). Moreover, the removal of potentially noncompliant participants eliminated the effect. The larger reduction in HDL cholesterol with the WG diet may be attributable to a combination of higher baseline concentrations in the WG group and a low-fat, weight-loss background diet (40). Low-fat (and low-saturated-fat) diets typically lower LDL cholesterol, but HDL cholesterol is reduced as well (41). To this point, LDL cholesterol decreased by ~12% in both groups. The effect of WGs on HDL cholesterol must be interpreted with caution, and future research is warranted. Indeed, MetS-related dyslipidemia did not improve or worsen with WG feeding in related clinical trials (13–16, 29).

A study limitation is the heterogeneous study population (different MetS criteria, both sexes, and women in varying hormonal states); however, there was an equal distribution between the groups for hormonal status and sex, and conclusions can be generalized to a broader population. Another limitation was the inability to maintain the baseline weights of participants during the “isocaloric” phase of the study. Providing a low-energy-dense, isocaloric diet to overweight and obese individuals often will cause a weight fluctuation of 1–2 kg in the first phase; thus, incorporating a run-in period may have ameliorated this issue. Those who took the compliance break had less favorable changes that, in a different setting, subjects in the WG group may have prolonged meals or consumed smaller portions because of increased satiety.

HDL cholesterol decreased more with the WG diet than with the RG diet in unadjusted and partially adjusted models; however, the decrease in and subsequent maintenance of HDL-cholesterol concentrations were parallel between the WG and RG groups (Supplemental Figure 1 under “Supplemental data” in the online issue). Moreover, the removal of potentially noncompliant participants eliminated the effect. The larger reduction in HDL cholesterol with the WG diet may be attributable to a combination of higher baseline concentrations in the WG group and a low-fat, weight-loss background diet (40). Low-fat (and low-saturated-fat) diets typically lower LDL cholesterol, but HDL cholesterol is reduced as well (41). To this point, LDL cholesterol decreased by ~12% in both groups. The effect of WGs on HDL cholesterol must be interpreted with caution, and future research is warranted. Indeed, MetS-related dyslipidemia did not improve or worsen with WG feeding in related clinical trials (13–16, 29).

A study limitation is the heterogeneous study population (different MetS criteria, both sexes, and women in varying hormonal states); however, there was an equal distribution between the groups for hormonal status and sex, and conclusions can be generalized to a broader population. Another limitation was the inability to maintain the baseline weights of participants during the “isocaloric” phase of the study. Providing a low-energy-dense, isocaloric diet to overweight and obese individuals often will cause a weight fluctuation of 1–2 kg in the first phase; thus, incorporating a run-in period may have ameliorated this issue. Those who took the compliance break had less favorable changes that, in a different setting, subjects in the WG group may have prolonged meals or consumed smaller portions because of increased satiety.

HDL cholesterol decreased more with the WG diet than with the RG diet in unadjusted and partially adjusted models; however, the decrease in and subsequent maintenance of HDL-cholesterol concentrations were parallel between the WG and RG groups (Supplemental Figure 1 under “Supplemental data” in the online issue). Moreover, the removal of potentially noncompliant participants eliminated the effect. The larger reduction in HDL cholesterol with the WG diet may be attributable to a combination of higher baseline concentrations in the WG group and a low-fat, weight-loss background diet (40). Low-fat (and low-saturated-fat) diets typically lower LDL cholesterol, but HDL cholesterol is reduced as well (41). To this point, LDL cholesterol decreased by ~12% in both groups. The effect of WGs on HDL cholesterol must be interpreted with caution, and future research is warranted. Indeed, MetS-related dyslipidemia did not improve or worsen with WG feeding in related clinical trials (13–16, 29).

A study limitation is the heterogeneous study population (different MetS criteria, both sexes, and women in varying hormonal states); however, there was an equal distribution between the groups for hormonal status and sex, and conclusions can be generalized to a broader population. Another limitation was the inability to maintain the baseline weights of participants during the “isocaloric” phase of the study. Providing a low-energy-dense, isocaloric diet to overweight and obese individuals often will cause a weight fluctuation of 1–2 kg in the first phase; thus, incorporating a run-in period may have ameliorated this issue. Those who took the compliance break had less favorable changes that, in a different setting, subjects in the WG group may have prolonged meals or consumed smaller portions because of increased satiety.
apparently large decrease in plasma alkylresorcinols on switching to the lower-energy diet may not only be explained just by the reduced intake of WGs.

The strengths of this study included a high level of participant adherence due to the controlled-feeding protocol and the use of commonly consumed WG products. Our study population is representative of the large sector of individuals in the United States who are highly vulnerable to metabolic diseases.

In conclusion, we showed that although replacing RGs with WGs within a weight-loss diet does not beneficially affect abdominal AT loss, it appears to be effective at normalizing blood glucose concentrations. Moreover, our findings indicate that WGs may improve glucose status in individuals with prediabetes and thereby prevent the onset of diabetes.

We thank our study participants and the research nursing staff at the Pennsylvania State University Clinical Research Center.

The authors’ responsibilities were as follows—PMK-E, JPVH, SGW, AMH, JAG, and SSJ designed the research; KJH and AMH conducted the research; SKL: supervised the MRI scanning and analysis; ABR: performed alkylresorcinol analysis; KJH and SGW: performed biochemical and statistical analyses; and KJH and PMK-E: wrote the manuscript. All of the authors take responsibility for the final content of the manuscript. SSJ worked for the Bell Institute of Health and Nutrition, part of the General Mills Company, and is now affiliated with Kerry Ingredients and Flavours; ABR worked for Bell Institute of Health and Nutrition, part of the General Mills Company, and is now affiliated with Chalmers University of Technology in Gothenburg, Sweden. Both companies produce a wide range of food products, including those that contain whole grains. None of the other authors declared a conflict of interest.

REFERENCES


27. Nilsson AC, Ostman EM, Granfeldt Y, Bjorck IM. Effect of cereal test breakfasts differing in glycemic index and content of indigestible


