Plasma Alkylresorcinols, Biomarkers of Whole-Grain Intake, Are Related to Lower BMI in Older Adults $^{1-3}$

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Abstract

Alkylresorcinols (AR) are phenolic lipids found in the bran fraction of whole-grain wheat, rye, and barley. In intervention studies, plasma AR concentration increased in response to greater intakes of whole grain, wheat, and rye. This study examined the cross-sectional associations between plasma AR and habitual whole-grain intake, BMI, and metabolic risk factors in 407 free-living older adults (166 men and 241 women; aged 60–81 y; median BMI: 27 kg/m$^2$). Plasma AR were measured by liquid chromatography–tandem MS, and whole-grain intakes were estimated by using an FFQ. After adjustment for fasting TG concentrations, median plasma AR concentrations across quartile categories of AR were 5, 14, 27, and 62 nmol/L, respectively. Spearman correlation coefficients between plasma AR and whole-grain wheat–rich foods and total bran intake were 0.31 and 0.27, respectively (both $P < 0.0001$). After adjustment for multiple covariates, the geometric means of BMI in the lowest and highest quartile category of plasma AR were 27.6 and 26.7 kg/m$^2$, respectively ($P$-trend = 0.04). No associations were observed between plasma AR and glucose and insulin. Our study shows a dose-dependent relationship between whole-grain intake and plasma AR and confirms the previously observed inverse relationship between whole-grain intake and BMI using an independent biomarker of whole-grain wheat intake. J. Nutr. 142: 1859–1864, 2012.

Introduction

In the past decade, accumulating evidence has indicated that consuming $\geq 3$ servings of whole grains per day is associated with improved metabolic disease risk markers and may be beneficial for body weight management (1). In the United States, ready-to-eat cereal and whole-wheat bread are major sources of whole grains; other important sources include oatmeal and popcorn (2). Assessment of whole-grain consumption largely relies on self-reported intake derived from FFQ or 24-h dietary recalls (1). Such dietary assessment instruments may be subject to memory bias (3), and estimates of intake may be hampered by participants’ difficulty in identifying and quantifying whole-grain foods (4). Incorporation of nonsubjective biomarkers of whole-grain intake in prospective and intervention studies may provide more valid estimates of intake and be used to independently confirm observed associations between self-reported estimates of whole-grain intake and health outcomes.

Recent intervention studies have shown that plasma concentrations of alkylresorcinols (AR; 1, 3-dihydroxy-5-alkylbenzene homologs) and their metabolites are biomarkers of whole-grain consumption (5–7), and recent evidence suggests that plasma AR concentrations are responsive to whole-grain wheat and rye intake (5,7). AR are found primarily in the bran fraction of certain whole grains (wheat, rye, and barley) (8), and once consumed, they are rapidly absorbed (9) and metabolized (10). It is estimated that the half-life of plasma AR is ~5 h (11), and thus plasma concentrations reflect the short-term intake of certain whole-grain foods. Intervention studies have shown that plasma AR are responsive to whole-grain wheat and rye intake (5,7), and recent evidence suggests that plasma AR concentration is moderately reproducible over 3–4-mo periods (7,12,13). Because major sources of AR, such as ready-to-eat cereal and whole-grain wheat bread, are usually consumed on a daily basis, plasma AR may be a useful marker of habitual consumption in populations with a stable intake of whole-grain foods. Al-
though, urinary AR metabolites have been correlated with whole-grain intake in the US populations (14,15), data on the use of plasma AR as surrogate biomarkers of total whole-grain intake in both elderly and free-living adults in the United States are scarce. In northern European populations who consume predominantly whole-grain rye, plasma AR has been found to correlate with intake of whole grain (16,17).

In the present study, we measured plasma AR concentration in a group of older American adults and examined the dose-response relationship between plasma AR and habitual whole-grain intake. In addition, we investigated the associations between plasma AR and BMI and metabolic risk factors. Our overall hypothesis was that higher plasma AR concentration, reflective of higher whole-grain wheat intake, should be associated with lower BMI and improved metabolic risk factors.

Participants and Methods

Study population. This study was an ancillary analysis using data from a vitamin K supplementation intervention study on age-related bone loss and vascular calcification in adults aged 60–80 y. In this double-blind, randomized controlled trial, participants were randomly assigned to either a vitamin K treatment group (daily multivitamin with 500 µg phylloquinone) or a control group (daily multivitamin without phylloquinone), as described elsewhere (18). After exclusion for bone and vascular health–related risk factors, a total of 452 free-living adults (185 men and 267 women) were enrolled in the study. For this analysis, we used blood and body composition measurements taken at 6 mo and dietary intake reported at 12 mo after baseline. Fasting plasma AR concentrations were measured in 413 of these participants. The final sample size was composed of 407 participants after the exclusion of individuals (n = 6) with missing data on either diet or physical activity. This study was approved by the Tufts Medical Center Institutional Review Board.

Plasma AR. At the 6-mo visit, blood samples were drawn between 0700 and 1000 after ≥10 h of fasting. Aliquots of EDTA plasma were stored at −80°C and protected from light until the time of analysis. Samples were shipped on dry ice to the Nestle´ Research Center, Lausanne, Switzerland, where they were immediately stored at −80°C until analysis. Plasma AR was measured and quantified with the use of normal-phase liquid chromatography-tandem MS (Waters Acquity UPLC system and Waters Quattro Premier XE triple quadrupole tandem mass spectrometer) (19). Concentrations of saturated AR homologs from C17:0 to C25:0 were quantified. Plasma total AR concentration (nmol/L) was used in this analysis. The interbatch CV for 2 different control plasma samples analyzed in triplicate with each batch were 8.3 and 12.6%, respectively.

Dietary intake. Habitual dietary intake was assessed by using the Harvard semiquantitative 126-item FFQ (20). The FFQ was mailed to participants to be completed at home, and the completed version was reviewed by a study team member during an appointment with participants. Diet was assessed with the FFQ at baseline and 1 y after enrollment into the trial. The FFQ consisted of a list of foods with their relative proportions as they exist in the intact caryopsis.” The reference amount commonly consumed (22). Whole-grain intake was subsequently expressed as grams per day. Because bran is a concentrated source of AR, our estimates of whole-grain intake were calculated by both including and excluding the component of added bran. Total bran (expressed as g/d) was calculated for both natural and added forms of bran. Additionally, we created a food group that captured primarily whole-grain wheat foods (g/d), such as whole-wheat breads and whole-grain ready-to-eat cold breakfast cereals for which the first ingredient listed on the food label was “whole wheat.”

Refined-grain foods (servings/d) were calculated by summing the intake of refined ready-to-eat cold breakfast cereals, white bread, English muffins/bagels or rolls, muffins/biscuits, white rice, pasta, pancakes/waffles, crackers, and pizza. Other dietary factors including total energy intake (kcal/d), fruit and vegetables (servings/d), fiber (g/d), magnesium (mg/d), and total folate (g/d) were also estimated from this FFQ. Because the FFQ is designed to capture habitual dietary intake over the previous year, estimates of diet that were obtained at 1 y after baseline were used for these analyses, thereby capturing the time frame in which the plasma AR measurements were taken. The time between blood sampling and administration of the FFQ was 6 mo. At the 1-y visit, −12% (n = 30) of study participants were missing an FFQ. In this case, dietary information from the baseline FFQ was imputed to maintain the sample size.

Body composition. At the same visit during which plasma samples were collected (6 mo after recruitment), body weight and height were measured by a nurse practitioner according to protocol. BMI was calculated as weight in kilograms divided by height in meters squared. Body trunk mass was measured by DXA scan using a GE Medical Systems Lunar Prodigy scanner (enCORE 2002 software, version 6.10.029). By using the estimates from the software for trunk lean mass and trunk fat mass, we calculated the percentage trunk fat. This measure is not a precise measure of abdominal adiposity (defined as the fat mass located between the upper edge of the second lumbar vertebra to above the iliac crest) as previously reported in a smaller sample of this cohort (n = 373) at baseline (19). However, there was a high correlation between the percentage trunk fat and abdominal adiposity at baseline (r = 0.86). Waist circumference measures were not obtained in this study.

Metabolic risk factor and covariate assessment. Fasting plasma glucose (mmol/L) was analyzed using the enzymatic kinetic method (hexokinase-UV/NAD, Olympus AU400 instrument with Olympus reagents; Olympus Diagnostics), and plasma insulin (pmol/L) was assessed using Human Insulin Specific RIA kits (Linco Research). Insulin resistance was defined as the homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated based on the model proposed by Matthews et al. (23). Plasma TG (mmol/L) were measured with a COBAS Mira (Roche Instruments). Smoking status (yes or no) and medication use (yes or no) including statins, hypoglycemic agents, and/or insulin at baseline were determined by questionnaire. Baseline physical activity level was assessed using the Physical Activity Scale for the Elderly score (24). Intakes of alcohol (g/d), fruit (servings/wk), and vegetables (servings/wk) were estimated from the FFQ.

Statistical analysis. To reduce skewness, a natural logarithmic transformation was applied to plasma AR, fasting TG, whole grains without added bran, whole grains with added bran, whole-grain wheat foods, total bran, refined-grain intake, alcohol intake, and BMI prior to formal analyses. Winsorization was applied to one extreme outlying value of TG are important predictors of plasma AR concentration (25,26). We calculated age, sex, and energy-adjusted means or geometric means for lifestyle and dietary characteristics across increasing quartile categories of plasma AR by

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using general linear models. To assess trends across quartile categories of plasma AR, we assigned the median plasma AR value of each quartile category to individuals within that category and then used the quartile median values as a continuous independent variable in the general linear models for continuous outcomes or in logistic models for dichotomous outcomes.

General linear models for ANCOVA were used to examine the associations between plasma AR and outcomes (i.e., BMI, percentage trunk fat, fasting glucose, fasting insulin, and HOMA-IR). The potential confounders controlled for in the model included sex, age, total energy intake, physical activity score, and randomization scheme of vitamin K supplementation. In a separate model, we further adjusted for smoking, alcohol, and fruit and vegetable intake to determine whether these associations were independent of other attributes of a healthy lifestyle. Analyses with glucose metabolism were performed after the exclusion of participants who were using diabetes medication (n = 20). We tested each association for effect modification by sex and found no evidence of interaction (all P > 0.2); thus, data are presented for both sexes combined. We also evaluated the associations between whole-grain intake (whole grains without added bran, whole grains with added bran, and whole-grain wheat foods) and BMI, percentage trunk fat, glucose, and insulin with general linear models using the same approach.

All correlation analyses are reported as Spearman rank-order correlation coefficients. Values in the text are means ± SD unless otherwise noted. The significance level was set as a 2-tailed P value < 0.05. Statistical analyses were conducted by using SAS statistical software (version 9.2; SAS Institute).

Results

The distribution of plasma AR was skewed (Figure 1). The 25, 50, and 75% percentiles of plasma AR were 9.3, 19.6, and 39.4 nmol/L, respectively. Participant characteristics are presented according to quartile categories of plasma AR (Table 1). Participants’ mean age was 68.3 ± 5.6 y, and their geometric mean of BMI was 27.5 ± 1.2 kg/m². Approximately 71% of the older adults in this sample were overweight or obese, and 5% were classified as having diabetes based on their use of glycemic control medicine. Plasma AR concentration was not associated with age or sex. Participants with higher plasma AR concentrations were less likely to be current smokers. Higher plasma AR concentration was associated with a higher percentage of energy intake from carbohydrate, a lower percentage of energy intake from fat, and higher intakes of magnesium, fiber, and folate. Plasma AR concentration was positively associated with self-reported intake of whole grains without added bran and with added bran, total bran, and whole-grain wheat foods. Participants in the higher quartile category of plasma AR concentration consumed slightly more fruit, but no relationship was observed with vegetable or refined grain intake.

Lipid-adjusted plasma AR concentrations were slightly but significantly correlated with intake of whole grains without added bran (Table 2). The correlation coefficient increased when added bran was also considered (whole grains plus added bran). The magnitude of the correlations with whole-grain wheat foods and total bran (natural and added bran) were larger than estimates of whole grains excluding bran (Table 2). No correlation was observed with refined-grain intake. The results were almost identical for unadjusted plasma AR concentrations.

After adjustment for age, sex, dietary and lifestyle factors, and randomization scheme, a significant inverse association was observed between plasma AR and BMI (26.5 vs. 25.7 kg/m² in the lowest compared with the highest quartile category of plasma AR; P-trend = 0.04), which was attenuated and no longer significant after use of diabetes medication was controlled for (P-trend = 0.12) (Table 3). Similarly, higher plasma AR concentrations were associated with significantly lower percentage trunk fat after potential confounding was controlled for (P-trend = 0.05); this association was attenuated and no longer significant after adjustment for diabetes medication (P-trend = 0.11) (Table 3). A significant inverse association was observed between plasma AR and HOMA-IR (P-trend = 0.05), but this association became nonsignificant after adjustment for BMI (P-trend = 0.16). The associations between plasma AR and fasting glucose and insulin were not significant. No associations were observed between estimates of whole-grain intake derived from the FFQ and fasting glucose, insulin, or HOMA-IR (data not shown).

Discussion

In this sample of older community-dwelling adults, a dose-dependent relationship was observed between whole-grain intake and plasma AR concentration. Furthermore, higher correlations between plasma AR and food groups rich in whole-grain wheat or bran-based foods confirm the specificity of plasma AR as a biomarker of these food sources. With the use of this independent biomarker, our results confirm our previous cross-sectional observation that higher consumption of whole-grain foods is associated with lower BMI in a dose-dependent manner (28). This inverse association is consistent with the observed beneficial association between whole-grain intake and body weight in other observational studies (29-31).

Although several studies have related estimates of whole-grain intake to concentrations of plasma AR, most of these studies were conducted in adults living in northern Europe where habitual whole-grain intake may be higher than in the United States (daily consumption <16 g or 1 serving) (33). For example, the mean intake of whole grains in a general Danish population was ~35 g/d (~2 servings) (12). Furthermore, the habitual intake of AR per capita in Nordic countries, estimated from national food supply and consumption data, was high, at ~20–40 mg/d (34). The generalization of plasma AR as a biomarker of whole-grain intake may be limited in populations who predominantly consume other types of whole grains such as oats or brown rice, and more specific biomarkers are needed for these cereals. In the United States, wheat is the main whole grain consumed (35). In our study, foods rich in whole-grain wheat, on average, contributed to half of total whole-grain consumption (data not shown). In the present study, the correlation coefficient...
coefficients, suggesting that although AR are transported in largely premenopausal. As in several previous studies (5,7), determinant of plasma AR (7,13), female participants were in those studies in which sex was found to be a significant because the moderate term reproducibility of AR is modest (13). The discrepancy from previous studies may be due to the fact that all female participants had been postmenopausal for not have significantly higher plasma AR concentrations (me-

TABLE 1 Characteristics of 407 older men and women by quartile (median) of plasma AR1

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4.8 nmol/L)</td>
<td>(14.3 nmol/L)</td>
<td>(27.0 nmol/L)</td>
<td>(61.5 nmol/L)</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>101</td>
<td>102</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>Age (adjusted for sex only), y</td>
<td>67.9 (66.6, 69.0)</td>
<td>67.9 (66.8, 68.9)</td>
<td>69.2 (68.1, 70.3)</td>
<td>68.7 (67.7, 69.8)</td>
</tr>
<tr>
<td>Male (adjusted for age only), %</td>
<td>36.2 (26.7, 45.7)</td>
<td>44.6 (35.2, 54.1)</td>
<td>32.7 (23.2, 42.1)</td>
<td>49.6 (40.1, 59.1)</td>
</tr>
<tr>
<td>PASE score2</td>
<td>126 (114, 137)</td>
<td>133 (122, 145)</td>
<td>132 (120, 143)</td>
<td>125 (114, 136)</td>
</tr>
<tr>
<td>Current smoker2, %</td>
<td>7.8 (3.4, 12.3)</td>
<td>6.7 (2.3, 11.1)</td>
<td>5.2 (0.8, 9.6)</td>
<td>1.9 (0.0, 6.3)</td>
</tr>
<tr>
<td>Diabetes medication use, %</td>
<td>8.9 (4.7, 13.1)</td>
<td>5.9 (1.7, 10.1)</td>
<td>4.9 (0.7, 9.1)</td>
<td>0.1 (0.0, 4.3)</td>
</tr>
<tr>
<td>Total energy, kcal/d</td>
<td>1694 (1578, 1810)</td>
<td>1748 (1633, 1862)</td>
<td>1782 (1645, 1878)</td>
<td>1706 (1592, 1820)</td>
</tr>
<tr>
<td>Total fat, % energy</td>
<td>33.9 (32.5, 35.4)</td>
<td>33.6 (32.2, 35.0)</td>
<td>32.9 (31.4, 34.3)</td>
<td>31.9 (29.3, 32.7)</td>
</tr>
<tr>
<td>Carbohydrate, % energy</td>
<td>48.5 (46.7, 50.3)</td>
<td>51.1 (49.3, 52.9)</td>
<td>51.7 (49.9, 53.5)</td>
<td>52.6 (50.8, 54.3)</td>
</tr>
<tr>
<td>Protein, % energy</td>
<td>18.7 (18.0, 19.4)</td>
<td>18.2 (17.5, 18.8)</td>
<td>18.0 (17.4, 18.7)</td>
<td>18.7 (18.0, 19.4)</td>
</tr>
<tr>
<td>Fiber2, g/d</td>
<td>17.4 (16.3, 18.5)</td>
<td>17.9 (16.8, 19.0)</td>
<td>18.6 (17.5, 19.7)</td>
<td>20.1 (19.0, 21.2)</td>
</tr>
<tr>
<td>Alcohol2,3, g/d</td>
<td>5.6 (4.3, 7.0)</td>
<td>5.6 (4.3, 7.0)</td>
<td>5.8 (4.5, 7.3)</td>
<td>5.8 (4.5, 7.3)</td>
</tr>
<tr>
<td>Magnesium2, mg/d</td>
<td>309 (297, 321)</td>
<td>314 (301, 326)</td>
<td>325 (313, 338)</td>
<td>348 (336, 360)</td>
</tr>
<tr>
<td>Folate2, μg/d</td>
<td>358 (334, 381)</td>
<td>378 (355, 401)</td>
<td>385 (363, 409)</td>
<td>422 (398, 445)</td>
</tr>
</tbody>
</table>

Food intake2
Whole-grain wheat–rich foods2,4, g/d | 2.1 (1.5, 2.7) | 2.9 (2.3, 3.7) | 4.4 (3.5, 5.4) | 5.3 (4.3, 6.5) | <0.0001 |
Whole grains without added bran3, g/d | 9.6 (8.0, 11.6) | 11.2 (9.3, 13.4) | 13.1 (10.9, 15.7) | 14.2 (11.9, 17.0) | 0.004 |
Whole grains with added bran4, g/d | 10.8 (9.0, 12.8) | 13.2 (11.1, 15.5) | 16.3 (13.7, 19.3) | 18.7 (15.9, 22.1) | <0.0001 |
Total bran4,5, g/d | 2.5 (2.0, 3.1) | 3.4 (2.8, 4.1) | 4.3 (3.6, 5.2) | 5.4 (4.5, 6.4) | <0.0001 |
Refined grains3,6, servings/d | 1.6 (1.4, 1.8) | 1.7 (1.5, 1.9) | 1.6 (1.4, 1.8) | 1.5 (1.3, 1.6) | 0.11 |
Fruit, servings/d | 2.3 (2.0, 2.6) | 2.1 (1.8, 2.4) | 2.3 (2.0, 2.6) | 2.6 (2.2, 2.8) | 0.06 |
Vegetables, servings/d | 3.1 (2.7, 3.4) | 3.1 (2.7, 3.4) | 3.1 (2.7, 3.4) | 3.2 (2.5, 3.5) | 0.52 |

1 Values are means and 95% CI unless otherwise indicated. AR, alkylresorcinol; PASE, Physical Activity Scale for the Elderly.
2 Adjusted for sex, age, and energy intake.
3 Values are geometric means and 95% CI.
4 Whole-grain wheat–rich foods include dark bread and whole-grain cold breakfast cereal with “whole wheat” as the first ingredient.
5 Total bran represents bran naturally present in whole grains and added bran.
6 Refined grain includes refined-grain cold breakfast cereals (<25% of whole grain or bran by weight), white bread, English muffins/bagels, muffins/biscuits, white rice, pasta, pancakes/crepes, crackers, and pizza.

between plasma AR and whole-grain wheat–based foods was 0.31. In other studies, reported correlation coefficients between plasma AR concentration and whole-grain intake ranged from 0.25 to 0.58, depending mostly on the dietary assessment tool used but also on study population, sample size, and type of study (i.e., observational or intervention) (27). In a large cohort of overweight participants undergoing a whole-grain–based intervention in the United Kingdom, the correlation between plasma AR and estimates of whole-grain intake derived from a general diet containing only refined grain in an intervention study (36). The median intake of whole grains without added bran estimated by the present FFQ was 14 g/d; however, this amount was similar to the mean whole-grain intake of ~12 g/d (or 0.77 serving/d) observed among older adults (aged ≥51 y) as reported in the NHANES 1999–2004 (33).

TABLE 2 Spearman correlation coefficients between plasma AR concentration and grain intakes in 407 older men and women1

<table>
<thead>
<tr>
<th>Quantitative estimates</th>
<th>rs</th>
<th>P</th>
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<tbody>
<tr>
<td>Whole-grain wheat–rich foods2, g/d</td>
<td>0.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Whole grains without added bran3, g/d</td>
<td>0.11</td>
<td>0.03</td>
</tr>
<tr>
<td>Whole grains with added bran3, g/d</td>
<td>0.18</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total bran4, g/d</td>
<td>0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Refined grain5, servings/d</td>
<td>−0.03</td>
<td>0.58</td>
</tr>
</tbody>
</table>

1 AR, alkylresorcinol.
2 Whole-grain wheat–rich foods include dark bread and whole-grain cold breakfast cereal with “whole wheat” as the first ingredient.
3 Whole grains: gram weight of whole-grain ingredients in all foods.
4 Total bran represents bran naturally present in whole grains and in added bran.
5 Refined grain includes refined-grain cold breakfast cereals (<25% of whole grain or bran by weight), white bread, English muffins/bagels, muffins/biscuits, white rice, pasta, pancakes/crepes, crackers, and pizza.
It is important to recognize the limitations of this study. First, its cross-sectional nature limits our ability to infer causality between biomarkers of dietary exposures and BMI. Second, only a single measure of plasma AR was available in this study and, thus, we were unable to examine the long-term reproducibility of plasma AR, although past studies have found repeated measures in free-living participants to be reproducible (7,12,13). Third, the percentage of trunk fat reflects the percentage of adipose tissue in the whole trunk region and this may not represent true intraabdominal adipose tissue, particularly in women. However, these results are consistent with the inverse association we previously observed between whole-grain intake and plasma AR and glucose metabolism. The lack of observed association may in part be due to a lack of power or that these older adults volunteering for this study were considered healthier than their peers, as they displayed relatively healthy metabolic profiles for individuals of their age and body weight. In addition, because individuals with bone or vascular ailments were excluded, our study sample may not reflect the general elderly population. Also, the majority of participants were white, which may have minimized possible confounding by race-ethnicity.

In conclusion, our results showed a dose-dependent relationship between whole-grain intake and plasma AR concentration and supported the inverse association between whole-grain intake and BMI. Further studies are needed to evaluate the application of plasma AR as a biomarker of whole-grain intake, particularly in more diverse populations who consume a greater range of whole grains, to understand if plasma AR can complement subjective measures of whole-grain intake.

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Literature Cited


