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Alkylresorcinol, a Biomarker for Whole Grain Intake, and its Association with Osteoarthritis: The MOST Study

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Abstract

INTRODUCTION: Higher intake of fiber has been associated with lower risk of incident symptomatic osteoarthritis (OA). We examined whether levels of alkylresorcinol (AR), a marker of whole grain intake, were associated with OA in subjects in The Multicenter Osteoarthritis (MOST) Study.

METHOD: Knee x-rays and knee pain were assessed at baseline and through 60-months. Stored baseline fasting plasma samples were analyzed for AR homologues (C17:0, C19:0, C21:0, C23:0, C25:0) and total AR levels (AR sum).

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AUTHOR CONTRIBUTIONS:

All authors qualify for authorship. Each author has participated sufficiently and made substantial contributions as follows:
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Alice H. Lichtenstein: Collection of data, analysis and interpretation of data, critical revision, final approval
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David Felson: Conception and design, analysis and interpretation of data, drafting of the article, obtaining of funding, statistical expertise, critical revision, final approval.
All authors take responsibility for the integrity of the work as a whole from inception to finished article.

CONFLICT OF INTEREST

The authors report no competing interests

Two nested case-control studies, one for incident radiographic OA and one for incident symptomatic OA were performed with participants re-assessed at 15, 30 and 60 months. Multivariable conditional logistic regression with baseline covariates including age, sex, BMI, physical activity, quadriceps strength, race, smoking, depressive symptoms, diabetes and knee injury tested the association of log transformed AR levels with OA outcomes.

RESULTS: Seven hundred seventy-seven subjects were, on average, in their 60's, and most were women. For 60-month cumulative incidence, there was no significant association between quartiles of AR concentration and incident radiographic (e.g., for incident radiographic OA, highest vs. lowest quartile of AR sum showed RR = 0.93 (95% CI 0.59, 1.47). and for symptomatic OA RR was 1.22 (95% CI 0.76, 1.94). In secondary analyses examining 30-month incidence, high AR levels were associated with a reduced risk of x-ray OA (RR = 0.31 (95% CI 0.15, 0.64).

CONCLUSION: In primary analyses, AR levels were not associated with risk of OA, but secondary analyses left open the possibility that high AR levels may protect against OA.

INTRODUCTION:

Whole grain wheat and rye cereal are major sources of dietary fiber. Wheat, in particular, is an important source of fiber in the US [1,2]. Published data demonstrates an independent effect of dietary fiber on several disease outcomes as well as on risk factors that lead to disease development. Whole grain wheat and bran cereals, and their fiber content have been consistently found to have protective effects against all-cause mortality [3,4], cardiovascular diseases (CVD) [5], development of type 2 diabetes [6,7], and colorectal cancer [8]. This effect is partly explained by lowering of BMI [9,10], cholesterol [11], and blood pressure [12], but emerging evidence points towards prevention and improvement in dysbiosis of the gut microbiota as a potential contributory mechanism.

Higher intakes of total fiber, especially fiber from cereal whole grains, have been associated with reduced risks of incident symptomatic osteoarthritis (OA) and worsening knee pain in large cohorts, even after adjustment for confounders such as body mass index (BMI). Dai et al, reported that total fiber, estimated from food frequency questionnaires (FFQs), was inversely associated with risk of symptomatic knee osteoarthritis (KOA) in both the Framingham Osteoarthritis Study and the Osteoarthritis Initiative (OAI) studies; showing significantly lower risk in the highest quartile of fiber intake compared to the lowest [13].

Fiber intake and its protective effect is potentially associated with changes in gastrointestinal microbiome, independent of BMI; as shown in a mouse model of high-fat diet induced obesity where dietary fiber was found to be protective against trauma-induced OA via restoration of healthy microbial gastrointestinal flora [14]. Boer et al, showed that abundance of Streptococcus species in the microbiome was associated with knee pain suggesting that this association was driven by local inflammation in the knee joint, making the gastrointestinal microbiome a possible therapeutic target for osteoarthritis-related knee pain [15].

The gut microbiome ferments dietary fiber and this affects release of short-chain fatty acids into the systemic circulation, influencing endogenous signals involved in lipid homeostasis and inflammation [16]. In humans, high-fiber diets reduce colorectal cancer risk and may also enhance response as an adjuvant to colorectal cancer treatment, potentially through regulation of gut microbiota [17]. Fiber intake affects the metabolic consequences of dysbiosis linked to type 2 diabetes and CVD. [18]. Since dietary fiber increases the relative abundance of beneficial anaerobic bacteria, increases butyrate fermentation, and has favorable metabolic effects reducing levels of systemic inflammation, it may affect the development of OA.

Biomarkers, as a proxy for dietary intake, can overcome misclassification of dietary exposure based on self-reported dietary intake. Alkylresorcinol (AR) is a phenolic lipid with odd numbered alkyl chains. Its five homologues (C17:0, C19:0, C21:0, C23:0, C25:0) are commonly found in the outer layer (bran) of wheat and rye grains [19,20]. The two dominant ARs are C21:0, C19:0, comprising on average 50% and 32% by weight in whole grain wheat respectively [21,22]. They are absorbed in the upper intestine, [19] are not affected by food processing, can be detected in the blood plasma, and remain stable in populations over long periods of time. Landberg et al, showed stable AR levels when comparing 2 different fasting AR measurements in 73 individuals 0.1 to 3.9 years apart. Also, no significant change was observed in a quality control sample analyzed over a period of 3 years [23]. Consistent high correlations are found between whole grain intake and C21:0 and other ARs [24,25] which have been validated in various populations [19,21,24,26–30]. Collectively, evidence points towards fasting plasma ARs levels as a reliable biomarker for habitual whole grain wheat and cereal fiber intake in populations with stable consumption of whole grain products.

Epidemiological studies have used ARs as biomarkers for dietary fiber from whole grain wheat, rye and cereal intake [20], and have shown inverse association to BMI [25,26], plasma lipid levels [28,31], colorectal cancer risk [32,33], and risk of type 2 diabetes [31,34].

Our hypothesis was that there would be an inverse relation between fasting plasma AR concentrations (as marker of whole grain intake), and rates of incident knee OA and/or knee pain in participants enrolled in The Multicenter Osteoarthritis (MOST) Study.

METHOD:

Study sample

The Multicenter Osteoarthritis (MOST) Study is an NIH-funded longitudinal observational study focused on symptomatic and radiographic knee OA. 3026 participants were enrolled from 2003–2006 and were examined at baseline and 15, 30 and 60 months after baseline [35].

Knee x-rays were obtained at baseline, repeated at 15, 30 and 60 months, and graded according to Kellgren-Lawrence (KL) grade [36].

BMI was calculated using measured weight in kilograms and height in meters.

Aliquots of plasma stored at −80’C from the baseline examination in MOST were sent to the Cardiovascular Nutrition laboratory at the Jean Mayer USDA Human Nutrition Research

Center on Aging at Tufts University, where they were analyzed for AR homologues and the sum of all homologues (AR sum) using an established (UPLC-QTOF-MS) method [37,38].

Analytic approach:

Focusing on MOST participants at risk of developing knee OA, two nested case-control studies were conducted, one for incident radiographic OA (new onset KL >= grade 2) and one for incident symptomatic OA (new combination of knee pain on most days + radiographic OA). For each of these outcomes, we excluded persons with this outcome at baseline. For example, for incident radiographic OA, we excluded subjects with prevalent radiographic knee OA (KL grade >=2) in at least one knee.

The relationship between baseline plasma ARs and incident OA was examined using a risk-set sampling strategy for control selection, where a set of controls who have not developed OA at each visit of 15, 30 and 60 months was selected. At each exam, we selected 2 controls for each case at random from those who had not developed the OA outcome.

Multivariable conditional logistic regression with covariates including age, sex, BMI, physical activity (using PASE [39]), isokinetic quadriceps strength [40], smoking status, depressive symptoms (using CES-D scale [41]), self-reported race, clinic site, diabetes and knee injury history was performed to examine the association of AR levels with incident OA outcomes up to 60 months.

We focused on the predominant AR homologues, C:19:0 and C:21:0 and also AR sum. Consistent with prior studies of AR levels [23,25,29,31] logarithmic transformation of AR levels was carried out to better approximate normal distributions. Quartiles based on sex-specific values were defined. Separate analyses were performed for each AR homologue concentration including C17:0, C19:0, C21:0, C23:0 and C25. Results are reported in quartile distribution of AR level. Analysis was also performed with AR as a continuous measure. In addition, we carried out stratified analyses to examine whether the association of AR levels with OA outcomes was different in obese vs. nonobese and male vs. female subjects.

Because of concerns that AR levels at baseline may not continue to have relevance to OA incidence at 60 months, we also carried out sensitivity analyses limiting incidence to 30-month follow-up. Sex-specific cumulative symptomatic and radiographic OA outcomes were also examined since AR levels can be affected by sex [23,25,28,42]. Levels of triglycerides and lipoprotein are involved in transport of ARs, and their levels may affect AR measures in plasma; therefore we carried out sensitivity analyses in which we adjusted additionally for baseline levels of these lipids.

RESULTS:

There were 258/260 cases and 514/518 controls in the studies of incident radiographic and symptomatic OA respectively. Participants were, on average, in their early 60’s, overweight, and mostly women. (Table 1).

We found no significant nor suggestive associations of AR C19:0, AR C21:0 or AR sum (C17:0 through AR C25:0) with 60-month incident radiographic OA, 60-month incident symptomatic OA (Figure 1a, 1b, Supplementary Tables 1 and 2). For example, for incident radiographic OA, highest vs. lowest quartile of the sum of AR's showed relative risk (RR) = 0.93 (95% CI 0.59, 1.47) and for incident symptomatic OA, RR = 1.22 (95% CI 0.76, 1.94) (figures 1a and 1b). No association of AR levels with OA was seen in women or men or in those who were obese vs. nonobese. Additional adjustment for triglycerides and LDL and HDL cholesterol did not affect results.

However, secondary analysis of 30-month outcomes showed that those with high AR levels had a lower incidence of radiographic OA (for AR sum, the relative risk of OA in the highest vs. lowest quartiles was 0.31 (95% CI 0.15, 0.64)) but not of symptomatic OA (relative risk 1.35 (95% CI 0.71, 2.59) (Table 2).

DISCUSSION:

To provide an objective assessment of whether a whole-grain enriched diet is associated with lower risk of OA or its progression, we measured plasma AR levels, a unique biomarker that reflects dietary fiber intake from whole wheat grain and cereals, in two nested case-control studies within the MOST cohort. Our primary results looking at cumulative outcomes up to 60 months do not support an association between AR levels and knee OA. However, secondary analysis of incident OA up to 30 months revealed an inverse association between AR levels and incident radiographic knee OA.

Randomized trials testing fiber and non-fiber intake, summarized in meta-analyses, have shown positive health effects in outcomes, such as lower blood pressure [43] a reduction in LDL and total cholesterol [44]; a reduction in CRP [45] and improved glycemic control among diabetics [46]. Clinical trials have also demonstrated the effect of fiber on weight loss [47,48], with significantly lower body weight, waist circumference, and BMI in the whole-grain wheat arm when compared to the refined grain arm [26].

As noted earlier, an inverse association between dietary cereal fiber intake and OA has been reported using food frequency data from the Osteoarthritis initiative and the Framingham Offspring cohorts [13]. However, food frequency questionnaires and other dietary surveys typically used in these studies are plagued by inaccurate recall of dietary intake. The measurement of plasma AR levels can avoid misclassification of fiber intake and has been shown to be associated with other diseases where fiber intake plays a role [31–34]. Thus, we expected to reduce errors of self-reported surveys, such as FFQs, by measuring AR levels at baseline to corroborating previous findings. An AR C17:0/C21:0 ratio of <0.2 indicates mainly wheat dietary intake (>0.6 ratio indicates mainly rye) [23]. The AR C17:0/C21:0 ratio for our cohort is 0.02, pointing towards whole grain wheat as the main component of whole grain fiber intake.

There are several factors that could be contributing to the null results of our primary analysis. Dietary fiber from whole wheat grain and cereal may not be associated with incident OA, or a single measurement of plasma ARs may not fully reflect fiber intake up to

60 months. Our sensitivity analysis revealed that those with higher AR levels had lower rates of radiographic but not symptomatic OA up to 30 months. From 30 to 60 months persons with high AR levels actually had a modest nonsignificant increased risk of OA (RR 1.4–1.6), explaining why positive findings at 30 months became null findings by 60 months.

The reason for the difference in effect of fiber intake in radiographic but not symptomatic OA is not obvious. Using food frequency questionnaires, Dai et al [13] showed a significant association between symptomatic OA and fiber intake but the association with radiographic OA remained unclear (subjects in OAI and Framingham cohorts were followed up to 48 months and 9 years respectively). If fiber intake has an effect on both progression and symptoms in OA, a delay in progression could explain the significant association at shorter follow up (30-months), while the benefit in pain may not become evident until later (years).

While AR is eliminated from plasma 24 hours after consumption [21], fasting plasma AR concentrations correlate well with fiber intake and have been shown to remain stable over 3.9 years in populations with stable diets [23]. Changes in diet could trigger changes in AR levels and this may underlie null findings that emerged between 30 and 60 months. Also, AR levels were measured in samples stored at −80 degrees for over 10 years. The stability of AR levels over this length of time is unknown, although fatty acids which are more sensitive than ARs, have documented stability for 8–12 years.

The MOST study did not include dietary intake questionnaires. We therefore did not adjust for energy intake; AR levels represent total fiber consumption rather than fiber as a proportion of the subjects' diet, which may have led to residual confounding. A higher proportion of fiber intake relative to the total diet may have different effects on the gut microbiome than absolute intake. Also, other factors not included in our analyses could have confounded our results.

In analyses of the OAI and Framingham Offspring cohorts, total fiber intake was subdivided into cereal, fruit and vegetable, and nut and legume fiber. The risk of symptomatic OA and knee pain worsening was found to be significantly lowered when comparing the highest to the lowest quartiles in total fiber intake. This correlates with our findings for incident radiographic OA at 30 months although it is not compatible with our null findings for symptomatic OA at 30 months.

The estimated daily fiber intake was 18.8 g (SD 7.8 g/day) in Framingham and is 15.0 g (SD 7.3 g/day) in OAI, close to the estimated daily US and European intake [49]. Given the lack of information on dietary data in the MOST cohort, we are unable to compare the fiber intake in MOST to OAI and Framingham. However, it must be noted that the total AR levels (AR sum) in our cohort were low compared to other populations (combined women and men AR mean level at baseline of 11.3 nmol/l in the MOST cohort vs 45.5 nmol/l and 38.5 nmol/l in European cohorts [23,32]).

While our primary analysis of incident OA up to 60 months was null, our 30-month results were positive at least for incident radiographic OA. We carried out this preplanned secondary analysis because of concern that dietary fiber intake reflected by AR levels may not be stable for 60 months. While these positive findings may point to a real protective

effect of fiber on the development of OA, our failure to find an association with symptomatic OA is concerning given the reported association of fiber with pain and symptoms. And we conducted a number of secondary analyses, raising the possibility that at least one might be positive. Ultimately, we are left with an uncertain but suggestive result.

In conclusion, in our nested case-control study, we did not observe any association between plasma AR levels at baseline and incident symptomatic or radiographic OA at 60 months. However, in secondary analysis in which cumulative OA incidence up to 30 months was examined, high levels of AR were associated with a. reduced risk of radiographic but not symptomatic OA. More evidence is necessary to clarify the association between cereal fiber intake and incidence and progression of symptomatic OA. Such evidence may be necessary before large scale randomized controlled trials are undertaken to test the efficacy of whole grain wheat and cereal intake modification or supplementation to prevent incidence and/or progression of symptomatic knee OA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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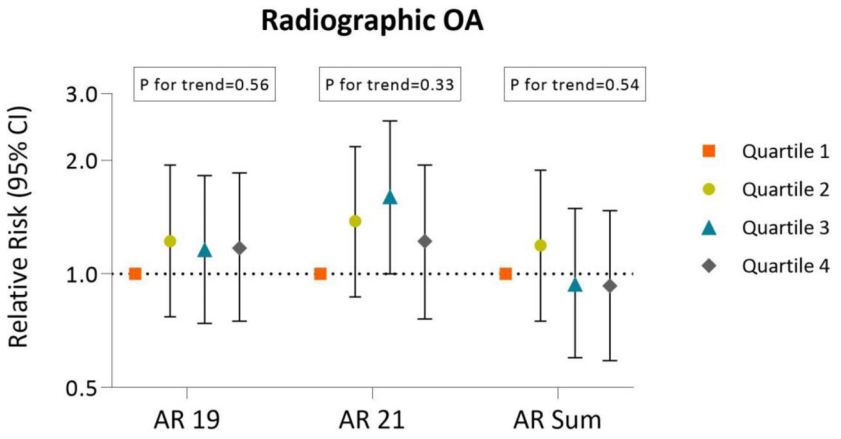
a



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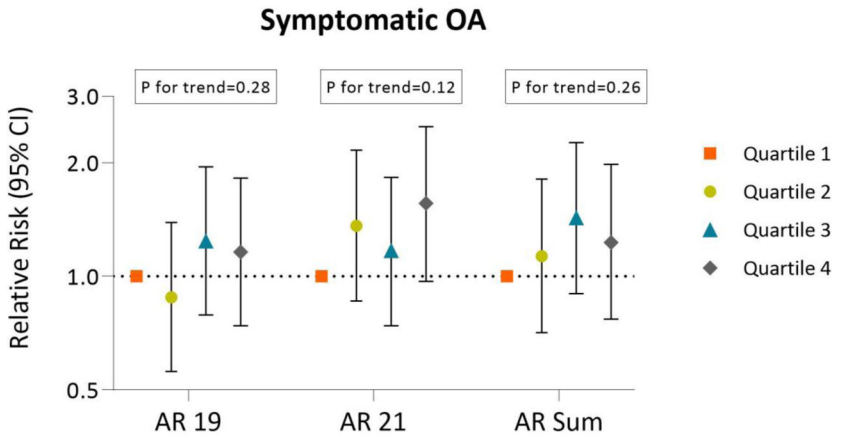

Figure 1.

Association of AR levels with Radiographic OA (a) and Symptomatic OA (b) up to 60 months. Multivariate conditional logistic regression for incidental Radiographic and Symptomatic OA with covariates including age, sex, BMI, physical activity, isokinetic quadriceps strength, race, diabetes, smoking status, depressive symptoms, and knee injury (by person). Abbreviations: AR (alkylresorcinol).

Table 1:

Baseline characteristics of MOST subjects by Case and Control Status and by Radiographic and Symptomatic OA analyses

	Radiographic OA		Symptomatic OA	
	Cases (n=258)	**Controls (n=516)**	**Cases (n=260)**	**Controls (n=518)**
Mean Age in years (SD)	61 (8.1)	60 (7.5)	63 (8.3)	62 (7.8)
% Female	61.3	60.4	63.1	55.7
Mean BMI (SD)	30.6 (5.2)	28.9 (4.7)	31.1 (5.5)	29.6 (5.2)
% Race	*Other:* 1.8	*Other:* 1.7	*Other:* 2.9	*Other:* 1.7
	African American: 13.9	*African American:* 10.6	*African American:* 12.4	*African American:* 11
	White: 84.3	*White:* 87.7	*White: 84.7*	*White:* 87.3
Mean PASE * (SD)	183.5 (88.7)	193 (87.8)	170.6 (85.3)	190.5 (84.7)
% Smoking Status	*Never: 53.3*	*Never:* 60.2	*Never:* 55.1	*Never:* 58.8
	Current: 4.4	*Current:* 5.4	*Current:* 6.6	*Current:* 5.6
	Former: 42.3	*Former:* 34.4	*Former:* 38.3	*Former:* 35.7
% Depressive Symptoms **	11	11	12	9.6
% Type 2 Diabetes	9.9	7.7	10.6	12.3
% Knee Surgery or Injury	37.2	34.2	43.8	45.5
Mean Quadriceps strength * (SD)**	85 (39.9)	87.9 (42.4)	78.1 (38.6)	88.9 (43.2)
Mean AR 17 nmol/l (SD)	0.08 (0.06)	0.08 (0.06)	0.08 (0.05)	0.07 (0.05)
Mean AR 19 nmol/l (SD)	0.9 (1.0)	0.9 (0.9)	0.9 (1.0)	0.8 (0.9)
Mean AR 21 nmol/l (SD)	4.4 (4.0)	4.6 (5.2)	4.8 (5.4)	4.2 (4.2)
Mean AR 23 nmol/l (SD)	3.6 (3.3)	4.0 (3.7)	3.7 (3.4)	3.7 (3.6)
Mean AR 25 nmol/l (SD)	2.1 (1.9)	2.3 (2.2)	2.3 (1.9)	2.1 (1.9)
Mean AR sum nmol/l (SD)	11 (7.1)	11.8 (9.0)	11.7 (8.1)	10.9 (7.6)

* Physical activity at baseline (Continuous PASE score)

** Depressive symptoms present if CES-D score >16

*** Mean quadriceps isokinetic strength in Newton meters.

Abbreviations: SD (standard deviation)

Table 2.

Cumulative incident Radiographic (*) and Symptomatic (**) OA up to 30 months by AR quartiles

		*Radiographic OA			**Symptomatic OA		
AR homologue	**Quartile**	**Case/Control$^{\gamma}$**	**Adj RR (95% CI)**	**P test for trend**	**Case/Control$^{\gamma}$**	**Adj RR (95% CI)**	**P test for trend**
AR 19	Q4 vs. Q1	25/68	0.73 (0.36, 1.47)		36/71	1.05 (0.57, 1.95)	
	Q3 vs. Q1	33/67	0.94 (0.48, 1.82)		38/69	1.07 (0.58, 1.95)	
	Q2 vs. Q1	36/52	1.53 (0.79, 2.98)		31/72	0.82 (0.44, 1.51)	
	Q1	30/59	1 (referent)	0.20	40/75	1 (referent)	0.68
AR 21	Q4 vs. Q1	20/66	0.60 (0.29, 1.25)		39/66	1.42 (0.75, 2.67)	
	Q3 vs. Q1	37/56	1.23 (0.63, 2.38)		37/83	1.01 (0.55, 1.85)	
	Q2 vs. Q1	37/65	1.11 (0.58, 2.12)		36/62	1.14 (0.61, 2.15)	
	Q1	30/59	1 (referent)	0.22	33/76	1 (referent)	0.37
AR sum ***	Q4 vs. Q1	20/69	0.31 (0.15, 0.64)		35/66	1.35 (0.71, 2.59)	
	Q3 vs. Q1	33/62	0.62 (0.32, 1.20)		39/70	1.40 (0.76, 2.61)	
	Q2 vs. Q1	32/67	0.60 (0.31, 1.16)		38/76	1.25 (0.67, 2.31)	
	Q1	39/48	1 (referent)	0.003	33/75	1 (referent)	0.32

*Adjusted for age, sex, BMI, race, physical activity at baseline, smoking status, study site, diabetes, quadriceps strength, and knee injury (by person)

**Adjusted for age, sex, BMI, race, physical activity at baseline, smoking status, depressive symptoms, study site, quadriceps strength and knee injury (per person)

***AR sum: log of sum (C17:0, C19:0, C21:0, C23:0, C25:0)

$^{\gamma}$Case control ratio for entire sample is 1:2.

Abbreviations: AR (alkylresorcinol), adj RR (adjusted relative risk)

AR measured in nmol/L.