

Association Between Dietary Intake of Antioxidants and Prevalence of Femoral Head Cartilage Defects and Bone Marrow Lesions in Community-based Adults

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ABSTRACT. Objective. Although there is evidence for a beneficial effect of dietary antioxidants on knee joint health, the data are sparse for the hip. Our aim was to examine the relationship between dietary antioxidants and early hip structural abnormalities in community-based adults.

Methods. The study included 214 participants without diagnosed hip osteoarthritis (OA) who underwent hip magnetic resonance imaging in 2009–2010. The prevalence of femoral head cartilage defects and bone marrow lesions (BML) was assessed. Intakes of antioxidant vitamins and their food sources were estimated from a food frequency questionnaire during 1990–1994.

Results. Higher intakes of Vitamin E (OR 0.63, 95% CI 0.41–0.96), lutein/zeaxanthin (OR 0.58, 95% CI 0.34–0.99), and lycopene (OR 0.64, 95% CI 0.44–0.95) were associated with a reduced prevalence of femoral head cartilage defects. Higher intakes of α -carotene (OR 0.42, 95% CI 0.19–0.94), β -carotene (OR 0.31, 95% CI 0.13–0.78), and lutein/zeaxanthin (OR 0.42, 95% CI 0.18–0.98) were associated with a reduced prevalence of femoral head BML. Higher vegetable consumption was associated with a reduced prevalence of femoral head cartilage defects (OR 0.65, 95% CI 0.46–0.91) and BML (OR 0.60, 95% CI 0.37–0.97).

Conclusion. Higher carotenoids intake and vegetable consumption were associated with reduced risk of hip cartilage defects and BML, and higher Vitamin E intake was associated with reduced risk of hip cartilage defects. These findings suggest a beneficial effect of dietary antioxidants on hip joint health. Although our findings need to be confirmed in other longitudinal studies, they suggest that the modification of dietary antioxidant intake may be a strategy for the prevention of hip OA. (J Rheumatol First Release August 1 2016; doi:10.3899/jrheum.160325)

Key Indexing Terms:

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HIP

Hip osteoarthritis (OA) is a significant public health problem, being a major cause of pain and disability¹. It is a prevalent chronic disease involving the whole joint with multifactorial etiology¹. Symptomatic hip OA represents a substantial

burden, with 1 in 4 people developing this condition in their lifetime². However, no current treatment slows the structural disease progression, and individuals with symptomatic endstage hip OA are eventually faced with hip replacement

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surgery as the only treatment option. Thus, preventive strategies are crucial to reduce the burden of the disease. Because diet is a universal population exposure, even a small effect that can be achieved by dietary manipulation may produce significant effects on public health.

Reactive oxygen species are generated by normal physiological processes within the joints, with excess reactive oxygen species being eliminated by natural antioxidants. High levels of oxidative stress (a measure of the overall reactive oxygen species status) are involved in the pathogenesis of OA, by oxidizing lipids and altering DNA and protein structure, leading to cell damage^{3,4,5}. Thus, suppressing the reactive oxygen species levels with appropriate dietary antioxidant supplements may provide a strategy to reduce the development and/or progression of OA. Vitamin C, Vitamin E, and carotenoids are antioxidants whose blood concentrations are primarily determined by dietary intake. At the knee, there is conflicting evidence for an association between dietary antioxidants and knee joint health and the progression of knee OA^{6,7,8,9}. While the Framingham OA Cohort Study reported that higher dietary intakes of Vitamin C, Vitamin E, and β -carotene reduced the progression of knee OA⁶, we found no effect of supplementary Vitamin E or dietary antioxidant vitamins on the progression of knee OA over 2 years^{7,8}. In healthy adults without clinical knee OA, we found higher dietary intakes of Vitamin C, and carotenoids were associated with better knee structural outcomes as assessed by magnetic resonance imaging (MRI)⁹. However, there is a paucity of data for the association between dietary antioxidants and hip joint health. In a large population-based cohort of female twins, high intake of fruit and vegetables was associated with reduced prevalence of radiographic hip OA¹⁰. Two randomized placebo-controlled trials evaluating the structural effect of avocado/soybean unsaponifiables in symptomatic hip OA did not demonstrate a clear structural effect, because no significant difference in joint space loss was shown between the intervention and control groups over 2–3 years^{11,12}. However, avocado/soybean unsaponifiables were found to reduce joint space loss in those with advanced joint space narrowing (JSN)¹¹ and to reduce the percentage of JSN progressors¹².

MRI facilitates direct and noninvasive examination of joint structures, identifying early structural changes that occur in healthy hips, prior to the presence of symptomatic or radiographic disease. Hip cartilage defects and bone marrow lesions (BML) represent early hip structural changes that are associated with hip OA¹³. In a cross-sectional study, we have shown that femoral head cartilage defects and BML are more common in people with diagnosed hip OA compared with those without, and the presence of femoral head cartilage defects and BML is associated with reduced femoral head cartilage volume¹³. Established risk factors for hip OA, such as occupational activity (weight lifting and stair climbing)

and fat mass, have been associated with increased prevalence of hip cartilage defects and BML^{14,15}.

No previous studies have examined the association between dietary antioxidants and early hip structural changes assessed from MRI in preclinical hip OA populations. Thus, the aim in our study was to examine the relationship between dietary antioxidants and hip cartilage defects and BML in community-based adults without clinical hip OA. Determining such relationships in a healthy population prior to the onset of clinical hip OA might help to better understand the pathogenesis of hip OA, and may potentially identify novel preventive strategies.

MATERIALS AND METHODS

Participants. The 214 participants were recruited in 2009–2010 from the Melbourne Collaborative Cohort Study (MCCS), a prospective cohort study of 41,514 residents of Melbourne, Australia. They were aged 27–75 years at recruitment (1990–1994)¹⁶. Because our intent was to investigate participants with no significant current or past hip disease, participants were eligible if they were aged 50–85 years without any of the following exclusion criteria: a diagnosis of hip OA made by a medical or allied health professional, significant hip pain lasting for > 24 h in the last 5 years, a previous hip injury requiring non-weight-bearing treatment for > 24 h or surgery (including arthroscopy), a malignancy, or a history of any form of arthritis diagnosed by a medical practitioner. A further exclusion criterion was a contraindication to MRI including pacemaker, metal sutures, presence of shrapnel or iron filings in the eye, or claustrophobia. The study was approved by the Cancer Council Victoria Human Research Ethics Committee (HREC 0707) and the Monash University Human Research Ethics Committee (CF07/3204 - 2007001712). All participants gave written informed consent.

Anthropometric data. At the time of MRI, height was measured using a stadiometer with shoes removed. Weight was measured using electronic scales with bulky clothing removed. Body mass index (BMI; kg/m²) was calculated.

Dietary data. At MCCS baseline (1990–1994), a 121-item food frequency questionnaire developed from a study of weighed food records¹⁷ was used to collect dietary data. Nutrient intakes were calculated from the food frequency questionnaire using Australian food composition data¹⁸, and using the US Department of Agriculture database for carotenoids¹⁹. Intakes of α -carotene, β -carotene, β -cryptoxanthin, and lycopene were measured separately, while intakes of lutein and zeaxanthin were combined because of the difficulty in separating the 2 carotenoids. All nutrient intakes reflected those from food only, without supplements. Fruits and vegetables are important food sources of Vitamin C and carotenoids^{20,21}, and thus they were chosen as potentially influential foods, and their intakes were assessed from the food frequency questionnaire¹⁷. Data on dietary supplements was collected by asking whether the participants took multivitamins, Vitamin A, Vitamin C, or Vitamin E at least once per week over the last 12 months.

Recreational physical activity. Recreational physical activity was assessed at the time of hip MRI using the Physical Activity Scale for the Elderly, a reliable and valid tool to assess physical activity in epidemiologic studies of older people²². Vigorous physical activity in the 7 days preceding MRI was assessed by asking whether a participant had performed at least 20 consecutive minutes of vigorous exercise severe enough to cause shortness of breath or sweating, with examples provided such as swimming, tennis, netball, athletics, and running.

Hip MRI and the measurement of hip cartilage defects and BML. Each participant had an MRI scan performed on their dominant hip in 2009–2010. The hips were imaged on a 3.0T whole-body magnetic resonance unit (Siemens, Verio, Siemens Medical) using a phased array flex coil in either of the 2 MRI centers. Coronal images were obtained using (1) a fat

saturation, proton density, spin echo acquisition sequence of repetition time 3370 ms, echo time 31 ms, flip angle 135°, slice thickness 2 mm, field of view 16 cm, pixel matrix 640 × 640, and 1 acquisition; or (2) a fat saturation, proton density, spin echo acquisition sequence of repetition time 3400 ms, echo time 64 ms, flip angle 90°, slice thickness 3 mm, field of view 13 cm, pixel matrix 256 × 256, and 1 acquisition. Sagittal images were obtained using (1) a fat saturation, proton density, turbo spin echo acquisition sequence (repetition time 2100 ms, echo time 31 ms, flip angle 135°, slice thickness 2 mm, field of view 16 cm, pixel matrix 640 × 640, and 1 acquisition) or (2) a T2-weighted fat-suppressed 3-D gradient-recalled acquisition sequence in the steady state (repetition time 14.45 ms, echo time 5.17 ms, flip angle 25°, slice thickness 1.5 mm, field of view 16 cm, pixel matrix 320 × 320, and 1 acquisition).

Femoral head cartilage defects and BML were assessed from coronal images and confirmed on sagittal images¹³. The presence of cartilage defects was defined as loss of cartilage thickness of more than 50%, which was shown on at least 2 consecutive slices. The presence of BML was defined as areas of increased signal intensity within the subchondral bone appearing on 2 or more consecutive slices. A musculoskeletal radiologist (YW) with over 15 years of experience in MRI structural outcome measurements in epidemiological studies supervised and independently monitored measurements. One trained observer (SS), who was blinded to participants' characteristics, assessed the presence of cartilage defects and BML for each participant in duplicate, at least 1 week apart. The intraobserver reproducibility (κ) was 0.82 for cartilage defects and 0.93 for BML.

Statistical analyses. The outcomes were the prevalence of cartilage defects and BML. Binary logistic regression models were constructed to analyze the relationship between dietary antioxidants and their food sources and the prevalence of cartilage defects and BML, adjusting for potential confounders of age, sex, BMI, energy intake, and vigorous physical activity. Age, sex, BMI, and vigorous physical activity are established risk factors for hip OA and have been associated with hip structural changes. It is generally accepted that associations between dietary nutrients and health endpoints should only be considered primary if the effects are independent of energy intake resulting from differences in body size, physical activity, and metabolic efficiency²³. Dietary intakes of antioxidants were standardized so that the OR would represent the effect of an SD increment in intake. Food intakes were divided into quartiles and assigned the median value for the quartile, hence OR reflect the odds associated with an increase of 1 serving per day in intake. P values of < 0.05 (2-tailed) were considered statistically significant. All statistical analyses were performed using Stata (Intercooled Stata 12, StataCorp LP).

RESULTS

The characteristics of the 214 study participants are presented in Table 1. The participants were aged 67.4 years on average with a mean BMI of 27.2 kg/m², and 55.6% were women. The prevalences of femoral head cartilage defects and BML were 29.9% and 12.2%, respectively.

Relationship between antioxidant vitamin intake and femoral head cartilage defects and BML. In univariate analysis, higher intakes of β -carotene ($p = 0.04$), lutein/zeaxanthin ($p = 0.02$), and lycopene ($p = 0.02$) were associated with a reduced prevalence of femoral head cartilage defects, with a trend toward significance for Vitamin E intake ($p = 0.06$; Table 2). After adjusting for energy intake, age, sex, BMI, and vigorous physical activity, higher intakes of Vitamin E (OR 0.63, 95% CI 0.41–0.96), lutein/zeaxanthin (OR 0.58, 95% CI 0.34–0.99), and lycopene (OR 0.64, 95% CI 0.44–0.95) were associated with a reduced prevalence of femoral head cartilage defects. There were no significant

Table 1. Characteristics of study participants (n = 214). Values are mean (SD) unless otherwise specified.

Characteristics	Values
Data collected at the time of hip MRI, 2009–2010	
Age, yrs	67.4 (7.7)
Female, n (%)	119 (55.6)
BMI, kg/m ²	27.2 (4.5)
Vigorous physical activity, n (%)	51 (23.8)
Prevalence of femoral head cartilage defects, n (%)	64 (29.9)
Prevalence of femoral head bone marrow lesions, n (%)	26 (12.2)
Dietary data collected at MCCA baseline, 1990–1994	
Vegetables, times/d, median (IQR)	5.0 (4.0–7.0)
Fruits, times/d, median (IQR)	3.5 (2.0–5.0)
Energy from dietary intake, kJ/d	9518 (2969)
Vitamin C, mg/d	213.4 (103.8)
Vitamin E, mg/d	8.4 (3.1)
Carotenoids	
α -carotene, mcg/d	2150.8 (1686.8)
β -carotene, mcg/d	6146.1 (4102.6)
β -cryptoxanthin, mcg/d	383.1 (286.9)
Lutein/zeaxanthin, mcg/d	3719.8 (2509.4)
Lycopene, mcg/d	7478.5 (4319.3)

MRI: magnetic resonance imaging; BMI: body mass index; IQR: interquartile range; MCCA: Melbourne Collaborative Cohort Study.

associations for Vitamin C, α -carotene, β -carotene, or β -cryptoxanthin intake.

In univariate analysis, higher intake of β -carotene was associated with a reduced prevalence of femoral head BML ($p = 0.03$) with a trend toward significance for α -carotene and lutein/zeaxanthin intakes (both $p = 0.07$; Table 2). After adjusting for confounders, higher intakes of α -carotene (OR 0.42, 95% CI 0.19–0.94), β -carotene (OR 0.31, 95% CI 0.13–0.78), and lutein/zeaxanthin (OR 0.42, 95% CI 0.18–0.98) were associated with a reduced prevalence of femoral head BML. There were no significant associations for Vitamin C, Vitamin E, β -cryptoxanthin, or lycopene intake.

Relationship between fruit and vegetable consumption and femoral head cartilage defects and BML. Higher vegetable consumption was associated with a reduced prevalence of femoral head cartilage defects (OR 0.65, 95% CI 0.46–0.91) and BML (OR 0.60, 95% CI 0.37–0.97) after adjusting for energy intake, age, sex, BMI, and vigorous physical activity. No significant association was observed for fruit consumption (Table 3).

Further adjustment for smoking, alcohol consumption, multivitamin supplements, and comorbidities (hypertension and diabetes) at MCCA baseline in our above analyses did not alter the results (data not shown).

DISCUSSION

In our study of community-based individuals without clinical hip disease, higher dietary intakes of carotenoids and vegetables were associated with reduced prevalence of

Table 2. Relationship between antioxidant vitamin intake and prevalence of femoral head cartilage defects and bone marrow lesions. Values are OR (95% CI) unless otherwise specified.

Variables	Univariate Analysis	p	Multivariate Analysis*	p
Cartilage defects				
Vitamin C	0.78 (0.57–1.08)	0.14	0.88 (0.60–1.30)	0.52
Vitamin E	0.74 (0.54–1.01)	0.06	0.63 (0.41–0.96)	0.03
α -carotene	0.76 (0.52–1.12)	0.17	0.81 (0.54–1.21)	0.30
β -carotene	0.60 (0.37–0.97)	0.04	0.65 (0.39–1.07)	0.09
β -cryptoxanthin	0.89 (0.66–1.21)	0.47	1.01 (0.72–1.42)	0.94
Lutein/zeaxanthin	0.54 (0.33–0.89)	0.02	0.58 (0.34–0.99)	0.04
Lycopene	0.65 (0.46–0.93)	0.02	0.64 (0.44–0.95)	0.03
Bone marrow lesions				
Vitamin C	0.80 (0.50–1.27)	0.35	0.74 (0.42–1.31)	0.31
Vitamin E	0.83 (0.54–1.28)	0.40	0.65 (0.37–1.16)	0.15
α -carotene	0.52 (0.26–1.04)	0.07	0.42 (0.19–0.94)	0.04
β -carotene	0.42 (0.19–0.92)	0.03	0.31 (0.13–0.78)	0.01
β -cryptoxanthin	1.00 (0.67–1.51)	0.99	1.07 (0.68–1.67)	0.78
Lutein/zeaxanthin	0.50 (0.24–1.05)	0.07	0.42 (0.18–0.98)	0.04
Lycopene	0.98 (0.65–1.49)	0.93	1.07 (0.69–1.67)	0.77

* OR of femoral head cartilage defects or bone marrow lesions being present per SD increase in vitamin intake adjusted for energy intake, age, sex, body mass index, and vigorous physical activity.

Table 3. Relationship between fruit and vegetable consumption and prevalence of femoral head cartilage defects and bone marrow lesions. Values are OR (95% CI) unless otherwise specified.

Variables	Univariate Analysis	p	Multivariate Analysis*	p
Cartilage defects				
Fruit	0.68 (0.51–0.92)	0.01	0.75 (0.54–1.03)	0.08
Vegetables	0.59 (0.43–0.81)	0.001	0.65 (0.46–0.91)	0.01
Bone marrow lesions				
Fruit	0.97 (0.65–1.45)	0.89	1.02 (0.66–1.58)	0.94
Vegetables	0.63 (0.41–0.97)	0.04	0.60 (0.37–0.97)	0.04

* OR of femoral head cartilage defects or bone marrow lesions being present per serving/day increase in fruit and vegetable intake adjusted for energy intake, age, sex, body mass index, and vigorous physical activity.

femoral head cartilage defects and BML, and higher intake of Vitamin E was associated with reduced prevalence of femoral head cartilage defects. These findings suggest a beneficial effect on hip cartilage and bone of these antioxidant vitamins obtained from vegetables.

While there is some evidence for a modifiable effect of dietary antioxidants on knee structure and knee OA, the evidence is limited with conflicting results reported by previous studies^{6,7,8,9}. While 1 study showed that higher dietary intakes of Vitamin C, Vitamin E, and β -carotene were associated with reduced progression of knee OA⁶, others found no association between supplementary Vitamin E or dietary antioxidant vitamins and the progression of knee OA^{7,8}. In community-based adults without clinical knee OA, we found that higher Vitamin C intake was associated with reduced presence of BML and lutein/zeaxanthin intake was associated with reduced prevalence of cartilage defects at the knee, suggesting a protective effect of dietary Vitamin C and carotenoids on articular cartilage and subchondral bone of

healthy knees⁹. There have been some studies examining the relationship of fruit, vegetable, and avocado/soybean unsaponifiables with structural changes in hip OA, indicating a potential structure-modifying effect on reducing the prevalence and progression of hip OA^{10,11,12}. Avocado/soybean unsaponifiables are a complex mixture of many compounds, with fat-soluble vitamins being only 1 among the multiple compounds. Although it is well known that fruits and vegetables are important food sources of Vitamin C and carotenoids^{20,21}, the identity of the active compound(s) in avocado/soybean unsaponifiables remains unknown. Further, there has been no study investigating the association between dietary antioxidants and early hip structural changes in pre-OA populations. In our current study of community-based participants free of clinical hip OA, we found protective associations of carotenoid and Vitamin E intake with early structural abnormalities at the hip assessed using MRI, including cartilage defects and BML. These features have been shown to be associated with the risk of hip OA and

established risk factors for hip OA^{13,14,15}. Consistent with vegetables being an important source of carotenoids, we also found that higher consumption of vegetables was associated with decreased prevalence of hip cartilage defects and BML. Taken together, our findings suggest a beneficial effect of antioxidant vitamins and vegetables on reducing the risk of hip OA.

Our study has a number of limitations. While the dietary intake of antioxidants and their food sources was measured in a valid fashion in our study^{24,25}, this was based on a single dietary assessment about 20 years prior to the assessment of outcomes, which may not reflect more recent and perhaps the cumulative intake over the time period, particularly if comorbidities or other lifestyle changes affect the intake. However, there is some evidence that nutrient intake is relatively stable and tends to be more stable with increasing age^{26,27}, such as in older individuals in our current study. Moreover, community-based people are more likely to move toward a healthier diet over time^{28,29}. This is likely to have caused underestimation of the strength of associations we observed. While dietary data collected 20 years earlier may have resulted in some misclassification of exposure, such misclassification is likely to have been nondifferential, and thus would have underestimated any observed associations. Further, our results persisted with additional adjustment for comorbidities. We have examined a healthy population without clinical hip OA, so the prevalences of hip cartilage defects and BML were not high. This may limit the power of our study to show significant results for some antioxidants such as β -carotene on cartilage defects and Vitamin E on BML, which showed some tendency toward a significant association in our study. Our study examined a community-based sample with no history of diagnosed hip disease. Although the results may not be generalizable to symptomatic populations, these findings are generalizable to populations that would be targeted by primary prevention strategies. Because the participants did not have symptoms, they are unlikely to have changed behaviors such as diet and physical activity because of hip disease. The prospective component of our study is a potential strength because a substantial period of time has elapsed between the ascertainment of exposure to dietary antioxidants and the assessment of outcomes, providing evidence for a possible cause-effect relationship between dietary antioxidant intake and hip structural changes.

The health of articular cartilage and subchondral bone depends upon the regular provision of nutrients, and there is evidence that diets deficient in nutrients may cause arthropathy³⁰. The effect of foods and dietary nutrients on joint structure is likely to be complex. The protective effect of carotenoids and Vitamin E on hip cartilage and subchondral bone may be attributable to their antioxidant effect. Oxidative stress has been identified as an important risk factor for OA, and reactive oxygen species, which are

generated by cells within joints, are involved in inflammation, cellular senescence, and apoptosis^{31,32}. Carotenoids and Vitamin E may inhibit these processes and thus reduce the likelihood of cartilage defects and BML. Although some supplements and drugs with antioxidant properties have been developed to enhance the cellular antioxidant status, the evidence is limited and inconsistent for the effect of antioxidant supply on preventing structural changes in OA³³. Our findings add to the literature, showing a protective effect of dietary antioxidants against hip cartilage and bone abnormalities that are associated with the risk of hip OA. Therefore, modification of dietary intake of antioxidants may be a strategy for the prevention of hip OA. Our findings also support the dietary recommendation to eat more vegetables. Further studies with a larger sample size and higher power will be required to verify the trends we have observed, and other longitudinal cohort studies will be needed to confirm these findings and strengthen the evidence for a causal relationship between dietary antioxidants and early hip structural abnormalities.

In community-based middle-aged and older adults without clinical hip disease, higher dietary intakes of carotenoids and Vitamin E and higher vegetable consumption were associated with reduced risk of hip cartilage defects and BML. These findings suggest a beneficial effect of dietary antioxidants on hip joint health and support the dietary recommendation for eating more vegetables. Although our findings need to be confirmed by larger cohort studies, they highlight the potential of modifying dietary antioxidant intake in the prevention of hip OA.

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