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ORIGINAL ARTICLE

Associations between dietary antioxidants intake and radiographic knee osteoarthritis

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Abstract The aim of the study is to examine the cross-sectional associations between dietary antioxidants (carotenoid, vitamin C, E, and selenium) intake and radiographic knee osteoarthritis (OA). A total of 4685 participants were included in this study. Dietary intake was assessed using a validated semi-quantitative food frequency questionnaire. Radiographic knee OA was defined as Kellgren-Lawrence (K-L) grade 2 in at least one leg. A multivariable logistic analysis model was established to test the relationship between dietary antioxidants (carotenoid, vitamin C, E, and selenium) intake and radiographic knee OA with adjustment of a number of potential confounding factors. A significant positive association between dietary vitamin C intake (*P* value for trend was 0.04 in multivariable adjusted analysis) and radiographic knee OA was observed. The relative odds of radiographic knee OA were increased by 0.39 times in the third quintile (OR 1.39, 95 % CI 1.11–1.73), 0.42 times in the fourth quintile (OR 1.42, 95 % CI 1.13–1.79), and 0.33 times in the fifth quintile (OR 1.33, 95 % CI 1.03–1.71). However, radiographic knee OA was not significantly associated with dietary carotenoid, vitamin E, and selenium. Among dietary antioxidants, dietary vitamin C intake was positively correlated with the prevalence of radiographic knee OA, while no significant association was found between dietary intake of carotenoid, vitamin E, and selenium and the prevalence of radiographic knee OA.

Keywords Carotenoid · Dietary antioxidants · Osteoarthritis · Selenium · Vitamin C · Vitamin E

Introduction

Osteoarthritis (OA) is a type of degenerative disease of the joints that occurs commonly in the middle-aged and older population with the knee being the most frequently affected site of all joints [1–4]. OA is one of the leading factors responsible for morbidity and can also lead to disability, thereby imposing significant impact on patients, caregivers, and medical costs [5]. Despite these concerns, the pathogenesis of OA is not yet entirely clear, and many factors may contribute to the variation in the occurrence and extent of the OA process.

One of the mechanisms in the development of OA is the damage to the articular cartilage induced by reactive oxygen species, which are generated by cells inside the joints and can cause oxidative damage to various macromolecules [6, 7]. The underlying mechanism has been attributed to the aging and degeneration of cartilage due to telomere instability of chondrocyte and downregulation of the chondrocyte function caused by oxidative stress [8, 9]. Cellular systems also play the role of antioxidant defense, in which enzymes and micronutrients can quench reactive oxygen species and increase the capability of anti-oxidation, thereby rendering these free species harmless [10]. The balance between prooxidant forces and antioxidant defense systems may influence the susceptibility of human body to prooxidant damage.

Vitamin C is a type of water-soluble vitamin with highly effective antioxidant properties due to its ability to react with

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numerous aqueous free radicals and reactive oxygen species (ROS) [11]. Carotenoids are a very important group of organic pigments with antioxidant properties [12]. Vitamin E is also known as a sort of potent antioxidant [13]. Selenium (Se) is a component of glutathioneper oxidase which protects macromolecules from oxidation stress [14]. Accumulated evidence has suggested that the consumption of antioxidant nutrients may influence the development and progression of OA. The longitudinal Framingham Osteoarthritis Study indicated that a higher level of self-reported dietary intake of vitamin C or β-carotene was associated with the reduced structural progression of knee OA, while dietary intake of vitamin E was unrelated to the progression of knee OA. Meanwhile, none of the micronutrients was associated with the incidence of radiographic knee OA [15]. Wang et al. found that the prevalence of subchondral bone marrow lesions was lower in the population with a greater vitamin C intake. Lutein and zeaxanthin intakes were associated with a decreased risk of cartilage defects, and β-cryptoxanthin intake was associated with a decreased tibial plateau bone area, suggesting a beneficial effect of these carotenoids on the knee cartilage and bone. The vitamin E intake, however, tends to be positively associated with the tibial plateau bone area, which is a negative effect on the bone [16]. The results of a cross-sectional study conducted by Muraki et al. showed that vitamin C intake was negatively associated with the minimum joint space width (mJSW) in the overall population. For the female subgroup, vitamin C intake appeared to be associated with mJSW, but not with the osteophyte area (OPA), while vitamin E intake was associated with OPA, but not with mJSW [17].

However, some other studies reported that antioxidant nutrients are not protective against the development and progression of OA. There was no significant differences between healthy and OA subjects in terms of the plasma and synovial fluid Se concentration [18]. Oka et al. found no association of dietary vitamin C/E intake with radiographic knee osteoarthritis in the Japanese elderly population [19]. The study conducted by Hill and Bird also reported no association between selenium-ACE supplementation and knee OA outcomes (pain, stiffness, and radiographic evidence of disease progression) [20]. Randomized, double-blind, placebo-controlled trials examining the effect of vitamin E supplementation (500 IU) on patients with knee indicated that, compared to placebo, supplemental vitamin E showed no significant effect on cartilage changes assessed over a 2-year period by MRI [21] or on the improvement of pain, stiffness, or physical function for 6 months [22]. Recently, a case-control study performed by Chaganti et al. revealed that higher levels of circulating vitamin C and E in plasma were not protective against incident radiographic knee OA and may be associated with an increased risk of knee OA instead [23].

Data reported in the literature are miscellaneous. Thus, it has great importance to clarify whether dietary antioxidants play a protective role against OA since diet and nutritional factors are modifiable. This study, therefore, aimed to investigate the association of the prevalence of radiographic knee OA with dietary antioxidant factors based on a self-administered brief diet history questionnaire (BDHQ) by setting up a cross-sectional study.

Materials and methods

This cross-sectional study was conducted in the Department of Health Examination Center, Xiangya Hospital, Central South University in Changsha, Hunan Province, China. The study design has been published previously [24]. We obtained approval for this study from the ethics committee at Xiangya Hospital, Central South University. Also, we obtained written informed consent from the participants in our study. Routine health checkups are very common in China, because the Chinese government encourages people to take periodic medical examinations. Registered nurses interviewed all participants during the examination using a standard questionnaire, with the purpose to collect information on demographic characteristics and health-related habits. Subjects were selected according to the following inclusion criteria: (1) 40 years old or above; (2) undergoing weight-bearing bilateral anteroposterior radiography of the knee; (3) availability of all basic characteristics including age, gender, body mass index (BMI), blood pressure etc.; (4) availability of biochemical test results; (5) completion of the semi-quantitative food frequency questionnaire (SFFQ) about the average consumption of foods and drinks over the past 1 year, and other information related to the living habits. In the beginning, this cross-sectional study included 9701 subjects who were undergoing routine checkups including weight-bearing bilateral anteroposterior radiography of the knee at the Department of Health Examination Center, Xiangya Hospital, Central South University in Changsha, Hunan Province, China, from October 2013 to July 2014. Firstly, subjects with other joint diseases with radiographic evidence, such as osteochondroma or other bone tumors, were excluded ($n = 105$). Then, 9371 individuals were available of basic characteristics, and 9224 of them were available of biochemical test results. Then, we excluded subjects under 40 years old ($n = 842$). Eventually, 4685 subjects completed the SFFQ, and they were included in the present study.

All subjects were undergoing weight-bearing bilateral anteroposterior radiography of the knee. Two orthopedists, without knowledge of participants' clinical symptoms, independently assessed all radiographs by using the Kellgren-Lawrence (K-L) radiographic atlas. All the radiographic interpretation was by consensus agreement. OA was divided into five categories according to the K-L grade: 0 = absence of OA, 1 = suspected OA, 2 = minimal OA, 3 = moderate OA, and 4 = severe joint OA [25]. If at least one knee joint was graded as K-L 2 or higher, the participant would be diagnosed with radiographic knee OA. The reliability of measurement was examined with an intraclass correlation coefficient (ICC), and the inter-rater and intra-rater reliability were both high ($\kappa = 0.86$ and 0.87, respectively).

Dietary intake was evaluated by using a semi-quantitative food frequency questionnaire (SFFQ) which was specially designed for the population in Hunan province of China. This SFFQ has been validated and used in a previously published study [26]. It contains 63 food items which are popularly consumed in Hunan province. Participants were requested to answer how frequently (never, once per month, two to three times per month, one to three times per week, four to five times per week, once per day, twice per day, or three times and above per day) they consumed each food item in the past year. There are six options for the average amount of food consumption in each time: less than 100 g, 100–200 g, 201–300 g, 301–400 g, 401–500 g, and more than 500 g. Color pictures showing food samples with labeled weights were given to participants as a reference. The SFFQ was answered in a self-administered way or completed through interviews by professional researchers. The Chinese Food Composition Table was referenced to calculate the individual composition of macronutrients and micronutrients of the included foods [27].

The weight and height of each subject were measured respectively to calculate the BMI. Participants were also asked about their average frequency of physical activity (never, one to two times per week, three to four times per week, five times and above per week) and average duration of physical activity (within half an hour, half an hour to 1 hour, 1 to 2 hours, more than 2 hours). Smoking and alcohol drinking status were asked face to face. The blood fasting glucose, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), and triglyceride (TG) were also detected on Beckman Coulter AU 5800 (Beckman Coulter Inc., Brea, CA, USA). Blood pressure was measured using an electronic sphygmomanometer. Subjects with the fasting glucose $\geq$ 7.0 mmol/L or currently undergoing drug treatment for blood glucose control were regarded as diabetes patients, and subjects with the systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg or currently using antihypertensive medication were regarded as hypertension patients.

The continuous data are expressed as mean ± standard deviation, and the category data are expressed in percentage. Differences in continuous data were evaluated by the Mann-Whitney *U* test, while differences in category data were assessed by the $\chi 2$ test. The dietary carotenoid, vitamin C, E, and selenium intake were classified into five categories based on the quintile distribution, respectively. The odds ratios (ORs) with 95 % confidence intervals (CIs) for the association between radiographic knee OA and dietary carotenoid, vitamin C, E, and selenium intake were calculated for each quintile of carotenoid, vitamin C, E, and selenium intake, and the quintile with the lowest value was regarded as the reference category. In order to calculate the adjusted OR of each quintile of carotenoid, vitamin C, E, and selenium intake, a multivariable model was adopted in the logistic analyses. Covariant variables include age, BMI (≥25, <25), gender (male, female), educational level (with or above high school, lower than high school), activity level, smoking status (yes, no), alcohol drinking status (yes, no), total energy intake (quintiles), fiber intake (quintiles), nutrients supplementation (yes, no), diabetes (yes, no), hypertension (yes, no), HDL-cholesterol, LDL-cholesterol, and triglyceride, and when we evaluated the association between one dietary antioxidant intake and knee OA, the other three antioxidants intakes were considered as covariates and included into the multi-variable model. Tests for linear trends were conducted based on logistic regression using a median variable of dietary intake level in each category. All data analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 17.0 (SPSS Inc., Chicago, IL, USA); a *P* value less than 0.05 was considered to be statistically significant.

Results

A total of 4685 participants (2451 males, 2234 females) aged from 40 to 85 years old were included in the present study. The basic characteristics of the study sample according to the knee OA status are illustrated in Table 1. Significant differences were observed between OA and non-OA subjects in terms of age, gender, BMI, activity level, nutrients supplementation, hypertension, and HDL-cholesterol.

The overall prevalence of knee OA in the sample of this cross-sectional study was 30.1 %. The average level of dietary carotenoid, vitamin C, vitamin E, and selenium intake were 4644.59 μg/day, 118.47 mg/day, 29.74 mg/day, and 43.77 μg/day, respectively. No significant association was found between dietary carotenoid intake and knee OA (*P* for trend = 0.52, Table 2). A significant positive association between vitamin C intake and knee OA was observed in the multi-variable adjusted model (Table 3). The relative odds of knee OA were increased by 0.39 times in the third quintile (OR 1.39, 95 % CI 1.11–1.73), 0.42 times in the fourth quintile (OR 1.42, 95 % CI 1.13–1.79), and 0.33 times in the fifth quintile (OR 1.33, 95 % CI 1.03–1.71), respectively. *P* for trend was 0.04. According to the multi-variable adjusted associations, dietary vitamin E (*P* for trend = 0.90) and selenium intake (*P* for trend = 0.90) were also uncorrelated with the prevalence of knee OA (Tables 4 and 5).

Table 1 Basic characteristics of the study population ($n = 4685$)

Basic characteristics	OA	Non-OA	*P*
N (%)	1411 (30.1 %)	3274 (69.9 %)	–
Age (years)	55.86 ± 8.19	51.84 ± 6.89	0.00
Sex (female, %)	44.8	48.9	0.01
BMI (kg/m^2)	24.75 ± 3.32	24.33 ± 3.14	0.00
Education background (with or above high school background, %)	46.8	46.9	0.99
Cigarette smoking (yes, %)	21.9	23.6	0.20
Alcohol drinking (yes, %)	35.9	36.1	0.87
Activity level (h/week)	2.51 ± 3.76	2.15 ± 3.41	0.04
Nutritional supplementary (yes, %)	38.0	33.5	0.00
Hypertension (yes, %)	36.5	31.5	0.00
Diabetes (yes, %)	11.0	9.1	0.05
Triglyceride (mmol/L)	1.91 ± 1.76	1.87 ± 1.78	0.20
HDL-C (mmol/L)	1.50 ± 0.38	1.53 ± 0.39	0.02
LDL-C (mmol/L)	2.98 ± 0.92	2.96 ± 0.94	0.46
Dietary intake			
Energy (Kcal/day)	1630.74 ± 795.09	1655.90 ± 783.95	0.48
Fiber (g/day)	17.97 ± 13.11	18.52 ± 14.50	0.70
Carotenoid (μg/day)	4568.95 ± 4083.04	4009.67 ± 4009.67	0.34
Vitamin C (mg/day)	117.14 ± 66.57	119.05 ± 76.99	0.52
Vitamin E (mg/day)	29.39 ± 13.41	29.88 ± 14.94	0.67
Selenium (μg/day)	43.37 ± 22.27	43.95 ± 22.74	0.77

Discussion

The present study evaluated the associations of dietary carotenoid, vitamin C, vitamin E, and selenium intake with the prevalence of radiographic knee OA. Out of these dietary antioxidants, vitamin C intake was found to be positively correlated with the prevalence of radiographic knee OA, while no significant association exists between dietary intake of carotenoid, vitamin E, and selenium, and the radiographic knee OA.

Different from some previous studies, the results of the present study did not meet the expectations that dietary antioxidant nutrients are protective against the development and progression of OA. Since evidence shows that ROS may be involved in the pathogenesis of OA [28], the theory that antioxidants vitamin C, alpha-tocopherol, and beta-carotene may

Table 2 Multivariable-adjusted association between dietary carotenoid intake and radiographic knee OA ($n = 4685$)

	Quintiles of dietary carotenoid intake					*P* for trend
	1 (lowest)	2	3	4	5 (highest)	
Median carotenoid intake (μg/day)	1143.70	2160.13	3371.75	5160.92	10883.40	–
Participants (*n*)	937	937	937	937	937	–
K-L Knee OA (*n*)	287	302	276	264	282	–
Multi-variable[a] adjusted ORs	Reference	0.97 (0.77, 1.21)	0.84 (0.65, 1.09)	0.76 (0.56, 1.04)	0.78 (0.53, 1.15)	0.52

Data are adjusted OR (95 % CI), unless otherwise indicated

n number, *OA* osteoarthritis

[a] Multi-variable model was adjusted for age, BMI (≥25, <25), gender (male, female), educational level (with or above high school, lower than high school), activity level, smoking status (yes, no), alcohol drinking status (yes, no), total energy intake (quintiles), fiber intake (quintiles), vitamin C intake (quintiles), vitamin E intake (quintiles), selenium intake (quintiles), nutrients supplementation (yes, no), diabetes (yes, no), hypertension (yes, no), HDL-cholesterol, LDL-cholesterol, and triglyceride

Table 3 Multivariable-adjusted association between dietary vitamin C intake and radiographic knee OA ($n = 4685$)

	Quintiles of dietary vitamin C intake					*P* for trend
	1 (lowest)	2	3	4	5 (highest)	
Median vitamin C intake (mg/day)	46.85	81.26	109.39	136.43	191.02	–
Participants (*n*)	937	937	937	937	937	–
K-L Knee OA (*n*)	258	289	296	297	271	–
Multi-variable[a] adjusted ORs	Reference	1.22 (0.98, 1.50)	1.39 (1.11, 1.73)*	1.42 (1.13, 1.79)*	1.33 (1.03, 1.71)*	0.04

Data are adjusted OR (95 % CI), unless otherwise indicated

n number, *OA* osteoarthritis

[a] Multi-variable model was adjusted for age, BMI (≥25, <25), gender (male, female), educational level (with or above high school, lower than high school), activity level, smoking status (yes, no), alcohol drinking status (yes, no), total energy intake (quintiles), fiber intake (quintiles), vitamin A intake (quintiles), vitamin E intake (quintiles), selenium intake (quintiles), nutrients supplementation (yes, no), diabetes (yes, no), hypertension (yes, no), HDL-cholesterol, LDL-cholesterol, and triglyceride

*$p < 0.05$, relative to the lowest intake category

play a role in the development mechanism of OA is biologically plausible. In addition to the antioxidant property, these nutrients may play the protective role against OA by other mechanisms. Vitamin C can stimulate the biosynthesis of collagen and aggrecan by articular chondrocytes in vitro [29–32], while vitamin E has been reported to possess anti-inflammatory properties [33]. However, not all studies suggest a protective effect of antioxidant nutrients on OA.

Similar to the finding of this study that vitamin C intake was positively correlated with the prevalence of knee OA, Chaganti et al. demonstrated that higher levels of plasma vitamin C were not protective against incident radiographic knee OA. On the contrary, subjects in the highest tertile vitamin C levels exhibited significantly increased odds to develop radiographic knee OA [23]. Kraus et al. evaluated the dose response of vitamin C with incident OA lesions in Hartley guinea pigs and found that Guinea pigs fed with a high concentration of vitamin C over 8 months showed a greater degree of proteoglycan loss, cartilage fibrillation, and osteophyte formation than the ones fed with a low concentration of vitamin C. The investigators postulated that the degenerative joint changes may be mediated partially by the local production of the transforming growth factor (TGF-beta), which was found to be actively expressed in the osteophytes of Guinea pigs fed with a higher concentration of vitamin C [34]. Furthermore, vitamin C can cross-link collagen and other proteins by the non-enzymatic glycation, which will lead to the formation of advanced glycation endproducts (AGEs) and therefore an increase of stiffness of the collagen network, which is hypothesized to enhance the susceptibility to OA. Another possibility is that antioxidant nutrients may impose a threshold for dietary intake to decrease the risk of knee OA. An excessive level of antioxidant nutrients intake may not reduce the risk of OA. Thus, this study meant to argue against the routine use of vitamin C supplementation for the prevention of knee OA. Patients need not consume vitamin C above the recommended daily value.

Table 4 Multivariable-adjusted association between dietary vitamin E intake and radiographic knee OA ($n = 4685$)

	Quintiles of dietary vitamin E intake					*P* for trend
	1 (lowest)	2	3	4	5 (highest)	
Median vitamin E intake (mg/day)	15.82	21.65	27.05	34.00	46.14	–
Participants (*n*)	937	938	936	937	937	–
K-L Knee OA (*n*)	283	301	248	309	270	–
Multi-variable[a] adjusted ORs	Reference	1.12 (0.90, 1.39)	0.94 (0.73, 1.20)	1.27 (0.95, 1.70)	1.03 (0.72, 1.47)	0.90

Data are adjusted OR (95 % CI), unless otherwise indicated

n number, *OA* osteoarthritis

[a] Multi-variable model was adjusted for age, BMI (≥25, <25), gender (male, female), educational level (with or above high school, lower than high school), activity level, smoking status (yes, no), alcohol drinking status (yes, no), total energy intake (quintiles), fiber intake (quintiles), vitamin A intake (quintiles), vitamin C intake (quintiles), selenium intake (quintiles), nutrients supplementation (yes, no), diabetes (yes, no), hypertension (yes, no), HDL-cholesterol, LDL-cholesterol, and triglyceride

Table 5 Multivariable-adjusted association between dietary Se intake and radiographic knee OA ($n = 4685$)

	Quintiles of dietary Se intake					*P* for trend
	1 (lowest)	2	3	4	5 (highest)	
Median vitamin Se intake (μg/day)	21.75	32.09	40.54	49.34	66.74	–
Participants (*n*)	938	936	937	937	937	–
K-L Knee OA (*n*)	271	297	278	293	272	–
Multi-variable[a] adjusted ORs	Reference	1.16 (0.93, 1.44)	1.05 (0.83, 1.34)	1.24 (0.93, 1.64)	1.07 (0.77, 1.48)	0.90

Data are adjusted OR (95 % CI), unless otherwise indicated

n number, *OA* osteoarthritis

[a] Multi-variable model was adjusted for age, BMI (≥25, <25), gender (male, female), educational level (with or above high school, lower than high school), activity level, smoking status (yes, no), alcohol drinking status (yes, no), total energy intake (quintiles), fiber intake (quintiles), vitamin A intake (quintiles), vitamin C intake (quintiles), vitamin E intake (quintiles), nutrients supplementation (yes, no), diabetes (yes, no), hypertension (yes, no), HDL-cholesterol, LDL-cholesterol and triglyceride

The present study found no significant association between dietary intake of carotenoid, vitamin E, and selenium, and the radiographic knee OA. The reason could be due to the intraarticular environment, which favors the execution of effect for water-soluble vitamin C, rather than fat-soluble agents such as beta carotene or vitamin E. Moreover, some evidences suggested that γ-tocopherol probably played a more important role than α-tocopherol in preventing specific types of oxidative damage [35, 36]. A cross-sectional investigation conducted by Seki et al. reported that high serum values of β-/γ-tocopherols were significantly associated with a low risk of radiographic knee osteoarthritis [37]. Therefore, it can be speculated that dietary intake of β-/γ-tocopherols or α-/γ-tocopherols, rather than the total vitamin E intake, may be effective in preventing specific types of oxidative damage. Carotenoids have been demonstrated to possess both antioxidant and prooxidant properties, depending on the oxygen pressure and the bioavailability of compounds inside the joint. Hence, the specific role of carotenoids with respect to knee OA is not clear yet [38]. As mentioned above, the complexity of the biological activity of antioxidant in vivo may lead to the complexity of the relationship between the pathogenesis of OA and dietary antioxidant consumption, and therefore further investigations are needed.

The present study has several strengths. Firstly, it was the first study conducted on a large sample of the Chinese population to explore the association of dietary intake of antioxidant nutrients with radiographic knee OA. Secondly, it was adjusted for a considerable number of potential confounding factors, especially for diabetes, hypertension, and some mineral intakes, which improved the reliability of the results greatly. Last but not the least, this study adopted FFQ, a valid and reliable method for evaluating nutrition intake, to measure dietary micronutrients consumption [39, 40]. Plenty of studies, including high-quality ones, adopted FFQ to measure food or nutrition intake [41, 42].

Several limitations of this study should be acknowledged. As a cross-sectional study, the definitive causal relation of this study could not be determined. Future prospective studies and intervention trials may be helpful for clarifying a causal association between dietary intake of antioxidant nutrient and knee OA. Meanwhile, there are also limitations inherent in the method of FFQ, even though it is a widely used and well-validated nutritional assessment instrument. FFQ is, by design, semi-quantitative in nature, so it cannot provide an absolute estimate of nutrient intake. In addition, it is difficult to determine whether the dietary measures of this study reflect the actual nutrient concentrations in the joint. The measure of dietary intake may be reflective of, but not necessarily specific to levels in the joint. Future studies should consider a more representative measure of antioxidant activity specific to the site of action.

Conclusion

This is the first epidemiological study that evaluated the association between dietary antioxidants and radiographic knee OA in the Chinese population, independent of some major confounding factors. Out of a variety of dietary antioxidants, vitamin C intake was positively correlated with the prevalence of radiographic knee OA, while no significant association was found between dietary intake of carotenoid, vitamin E, and selenium, and the prevalence of radiographic knee OA.

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Compliance with ethical standards

Disclosures None.

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