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Dietary and supplemental vitamin C and D on symptom severity and physical function in knee osteoarthritis

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Abstract

Purpose: Vitamins C and D have been associated with decreasing pain and increasing function but these associations are not definitive. This cross-sectional study explores what relationships supplemental and dietary intake of vitamins C and D have on pain severity and physical function in patients with knee osteoarthritis.

Methods: Using data from the Osteoarthritis Initiative, we performed regression analyses to examine relationships between vitamins C and D, pain, and function. Dietary vitamin D and dietary vitamin C were divided into >90th, 50–90th, <50th percentile. The high percentile group for supplemental vitamin D was divided into >85th percentile whereas the high percentile group for supplemental vitamin C was divided into >90th percentile.

Results: We found the 90th/85th percentile levels of dietary and supplemental vitamin D to be positively associated with pain ($\beta=0.180$; $p=0.028$) and inversely related to physical function ($\beta=-0.150$, $p=0.028$), respectively. Daily intake of vitamin C showed no statistical significance.

Conclusions: We found that supplementary vitamin D was strongly associated with lessened disability for knee OA patients. The unexpected finding that associated dietary vitamin D with greater knee pain merits further study.

Keywords

Osteoarthritis; Nutrition; Physical Function; Vitamin C; Vitamin D

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to disclose.

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INTRODUCTION

Osteoarthritis (OA) is a progressive disease mainly affecting the hyaline articular cartilage of the knees, hips, fingers, and lower spine. Risk factors include sex, race, genetic factors, occupation, nutritional intake, joint trauma, malalignment, proprioceptive deficiencies, and obesity (1, 2). Pain is often reported as the key motivating factor for patients to seek medical care for OA, and is an important precursor to disability (2). Epidemiologically, OA is the most common type of arthritis affecting older adults (3). According to the Centers for Disease Control, 80% of those with OA will have limitations in movement and 25% cannot perform their activities of daily living, with 11% of affected adults needing help with self-care and 14% requiring assistance with routine needs (3, 4). Given that there are no curative treatments, current management of OA remains focused on the alleviation of pain and prevention of further losses in physical function.

Some studies have specifically focused on vitamins C and D, which are micronutrients that may be associated with pain and physical function. There have been varying results in regards to whether or not these nutrients have any effect. One area of research has focused specifically on nutrient deficiencies. A recent review article reported that a 5-year longitudinal study found an association between vitamin D and pain (5), specifically that moderate vitamin D deficiency predicted both knee and hip pain as measured by vitamin D serum levels (25-hydroxyvitamin D). Additionally, a questionnaire-based study also found an association between vitamin D and pain where experimental pain and self-reported measures among subjects with lower serum levels of vitamin D were associated with greater clinical pain, especially for African Americans compared to Caucasians (6).

Other research has looked at the effects of dietary supplementation. Studies on vitamin D showed that deficiency increases the risk of knee osteoarthritis progression which may be improved through supplementation (7–9). One pilot study on diet elucidated that low intake of vitamins C and D are the most significant risk factors of OA (10). However, studies examining vitamin D intake and osteoarthritis pain reveal conflicting results, with some studies demonstrating minor to no benefit for pain outcomes (5, 8, 11). For example, a study examining 36,282 participants from the Women's Health Initiative randomized trial found vitamin D did not have an association with the frequency or severity of joint symptoms (12). One randomized controlled pilot study consisting of 107 patients, who were given vitamin D or a placebo over a 12 month period, found little to no effect of Vitamin D on pain and functional disability (11). The study looked at the The Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scales but was a randomized controlled trial that focused on biochemical parameters of total vitamin D intake. Similarly, another study found no association between radiographic knee OA and vitamin D levels (18). More specifically, the study examined the Hertfordshire Cohort and found that high tertile vitamin D levels (>51.5 nmol/l) were not associated with knee pain. Some have reported that vitamin C intake can effectively reduce osteoarthritis pain, but only under conditions where high doses (average 430mg daily for men, 501mg daily for women) were ingested (5, 13, 14). Vitamin C has also been shown to reduce risk for radiographic OA when intake was in the upper tertile (10, 14). However, a recent systematic review reported conflicting evidence

from several studies that either showed an association or no association between vitamin C intake and OA (5).

Given the variability in evidence for the relationship between nutritional status of vitamins C and D, knee pain severity, and physical function in persons with knee OA, this study aimed to further examine what types (dietary compared to supplemental) and at what levels these micronutrients are associated with osteoarthritic pain as well as physical function.

MATERIALS AND METHODS

Data

Data for the study were obtained from the Osteoarthritis Initiative (OAI), a prospective, longitudinal, observational cohort study mainly comprised of persons who currently suffer from or are at high risk for knee OA. Data were collected from knee OA subjects who completed questionnaires at four designated OAI clinical research facilities. More specifically, dietary intake data were obtained from a food questionnaire, known as the Brief Block Food Frequency Questionnaire which was developed from the National Health and Nutrition Examination Survey (NHANES) III. These multi-centered data were gathered from four sites; Ohio State University, University of Maryland/Johns Hopkins University, Brown University/Memorial Hospital of Rhode Island, and University of California, San Francisco. Funding for the OAI came from National Institutes of Health (NIH) as well as several pharmaceutical companies. A total of 4,796 men and women aged 45–79 years were enrolled into the study primarily consisting of those with knee OA and those at high risk for developing knee OA. Two subcohorts, an incident group and a progression group, were included in the OAI. Our study focused on the progression subcohort, which consisted of 1,390 subjects with knee OA, defined as having both frequent knee symptoms on most days for at least one month during the past year and radiographic tibiofemoral knee OA in at least one knee. Knee symptoms are defined as pain, aching, or stiffness around the knee and radiographic knee OA is defined by definite tibiofemoral osteophytes. The incidence subcohort consisted of 3,284 participants at high risk for knee OA. There were 122 subjects placed into a non-exposed control group. Additional protocol details are published and available on the internet (<https://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf>) (15). Specific data sets for the analysis included version 0.2.2 of Nutrition (Nutrition00), Joint symptoms/function (JointSx00), and Subject characteristics and Risk Factors (SubjectChar00). The nutrition status variables selected were V00DTVITC (dietary vitamin C), V00SUPVITC (supplemental vitamin C), V00DTVITD (dietary vitamin D), and V00SUPVITD (supplemental vitamin D). Potential risk factors selected were: age, sex, race, BMI, and comorbidities. BMI was measured in kg/m². Comorbidities (COMORB) were defined by a score from a self-reported version of the Charlson comorbidity index. These variables selected were based on prior literature review (7, 10, 14).

Analytical Approach

Demographics—Sample demographics and nutrients were examined using mean, standard deviation, proportion, and correlation using SPSS 22. Risk factors such as age, gender, race, BMI, and comorbidities were controlled in the analysis. The score for the

modified Charlson comorbidity index used to measure comorbidities ranged from 0 to 10 based on the number of conditions and condition severity the patient reported. Specifically, conditions included cardiovascular disease, asthma, and asthma severity. Supplementary vitamin intake was also adjusted for dietary vitamin intake and vice versa. Our study specifically focused on the progression subcohort at baseline. Participants with missing data on dietary or supplemental intake from vitamins C and D were excluded.

Nutrition—Nutritional factors investigated were vitamins C (mg) and D (IU), and their status was defined by average daily nutrients from supplements and food. Supplemental and dietary vitamin C was measured in mg, ranging from 0 to 3,810 mg and 4.50 to 654.90 mg, respectively. The ranges for supplemental and dietary vitamin D were 0 to 600 IU and 4.38 to 1002.34 IU, respectively. Cutoffs for dietary and supplemental vitamin were divided into high percentile intake (>90th percentile), mid percentile intake (50–90th percentile), and low percentile intake (<50th percentile). Due to the lack of variations in supplemental vitamin D intake at >90th percentile, high dose cutoff for supplemental vitamin D was defined as those >85th percentile. These cut-off levels were selected to better discriminate the varying levels of vitamins since the distributions of vitamin intake in our sample were skewed. To make the sample groups more balanced, the cut-off levels were therefore selected.

Pain and Function—Pain severity was operationally defined using the WOMAC pain subscale. These scores are based on a continuous scale of 0–20 with 0 defined as “no activity related pain” and 20 as “severe activity-related pain.” Questions include, ‘How often do you experience knee pain?’ with 5 answer options (never; monthly; weekly; daily; always). Pain questions were specifically related to movement, for example, ‘What amount of knee pain have you experienced in the last week during the following activities?’ Movements included in the question list included twisting/pivoting on your knee; straightening knee fully; bending knee fully; etc. with 5 response options (none; mild; moderate; severe; extreme). Physical function was operationally defined by the WOMAC disability subscale scores, which range from 0–68 with 0 defined as normal function and 68 as severely affected function. Respondents were asked to indicate the degree of difficulty experienced in the last week due to knee discomfort and examples of the areas of function queried include, ‘ascending stairs; rising from sitting; standing; bending to floor/pick up an object; etc.’ with 5 response options (none; mild; moderate; severe; extreme). Two composite variables were created to assess pain severity and physical function level. Pain severity and physical function were not specific to the right or left knee.

Data Analysis—Univariate analysis was first performed to elucidate an association between independent variables (vitamins C and D intake) at different cutoffs and outcome variables (pain and physical function). A strong association was defined as $\beta \geq 0.1$, moderate association (β is between 0.05 and 0.1), and weak association ($\beta < 0.05$). Spearman correlation was calculated between dietary/supplemental vitamin C and D intake, function, pain, demographic characteristics, and comorbidities to select significant covariates adjusting for pain and function. Multivariate regression was subsequently performed to control for these covariates. All statistical tests were set at an alpha level of 0.05.

RESULTS

Our analysis of the progression subcohort included a total of 592 (43.1%) men and 781 (56.9%) women with symptomatic knee OA (total $n=1,373$). Average age of the participants was 61.5 years (SD, 9.5 years; range, 45–79 years). The majority of the participants were Caucasian ($n=970$; 70.6%) and African American ($n=361$; 23.6%) (Table 1). Most of the applicants had no comorbidities ($n=947$; 69.0%), a comorbidity index score of 1 ($n=248$; 18.1%), or a comorbidity index score of 2 ($n=108$; 7.9%). The remainder either had an index score greater than 3 or had missing data and comprised less than 5% of the participants. Supplementary intake of vitamin C ranged from 0 to 3,810 mg while dietary intake was 4.5–654.9 mg, with Institute of Medicine recommendations of dietary intake of 75 mg for women aged 19 and older (non-pregnant or non-lactating) and 90 mg for men in the same age group (16). Vitamin D supplementation ranged from 0 to 600 IU while dietary intake of vitamin D ranged from 4.38 – 1,002.3 IU. The recommended dietary allowance for vitamin D varies by age and ranges from 600–800 IU in adults (17). Summary statistics for high, mid, and low percentile of dietary and supplemental vitamins C and D can be found in table 2. High percentile intake for vitamin C was >204mg for diet and >931.9mg for supplements. Mid percentile intake vitamin C levels showed 100.3–204mg for diet and 60.0–931.9mg for supplements while low percentile vitamin C intake showed <100.3mg for diet and <60mg for supplementation. High, mid, and low percentile cutoff values for dietary vitamin D are >271.2IU, 104.6–271.2IU, and <104.6, respectively. High percentile dose cutoff for supplemental vitamin D was >400IU. Cutoffs for mid and low percentile dose supplemental vitamin D intake was 200–400IU and <200IU, respectively.

Results for the univariate analysis are summarized in table 3. In the low percentile, dietary vitamin C has a significant and strong negative association with pain ($\beta = -0.095$ $p=0.013$). However, dietary vitamin C in the low percentile was not associated with pain after adjustment for risk factors ($p=0.066$) (Table 4).

When dietary intake of vitamin D was in the highest percentile range (>90th percentile), vitamin D had a significant positive association with pain ($\beta = 0.238$; $p=0.005$). The association remained significant after adjusting for risk factors ($\beta=0.18$; $p=0.028$). Persons with high and mid percentile dietary intake of vitamin D had a significant association with function (High: $\beta=0.192$; $p=0.025$, Mid: $\beta=-0.09$; $p=0.038$). However, neither remained significant with function after risk adjustment ($p=0.067$ and $p=0.099$, respectively).

There was a negative association between supplemental vitamin D intake and physical function in the >85th percentile, showing that taking more than 400IU was associated with less physical function ($\beta=-0.18$; $p=0.011$). This remained significant after risk adjustment ($\beta=-0.15$; $p=0.028$).

WOMAC pain scores for all participants (mean = 4.25, SD = 3.30) ranged from a minimum of 0 to a maximum of 19.50. WOMAC function scores (mean = 14.31, SD = 11.55) ranged from a minimum of 0 to a maximum 67.47. Those in the >90th percentile for dietary vitamin C had the highest average pain and function scores of 5.41 and 18.75, respectively. Table 5

outlines the full summary statistics of WOMAC pain and function scores for each micronutrient.

DISCUSSION

This is a cross-sectional study intended to evaluate the associations of supplemental and dietary intake of vitamins C and D on pain severity and physical function in patients with knee OA. Results from this study suggest there is a significant association between high levels of dietary vitamin D and higher pain levels. There was also an association between high supplemental vitamin D levels and better function even after adjusting for age, sex, race, comorbidities, and BMI. The results also suggest a marginally significant association between high percentile dietary intake of vitamin C and pain as well as a marginally significant negative association with low percentile dietary vitamin C and physical function.

Our findings support prior studies indicating that high levels of vitamin D are associated with physical function (5, 7, 14, 18–20). In particular, our findings support research demonstrating a positive relationship between supplemental vitamin D and improved physical function. A recent study conducted by Raczkiwicz and colleagues compared rheumatoid arthritis patients to a control group of 28 osteoarthritis patients. The results concluded that higher Vitamin D intake was associated with physical activity and better quality of life (21).

As opposed to some studies (8, 11, 12), we found a correlation suggesting that higher intake of dietary vitamin D is associated with higher levels of pain. Because of the cross-sectional nature of the data, we cannot determine causality or directionality in the association. It is possible that patients with greater severity of OA knee pain may have been instructed to increase their intake of foods with vitamin D to help relieve their symptoms based on previously identified associations (22). Additionally, patients deficient in Vitamin D may experience increased sensitivity to pain as previously mentioned and may consequently alter their behavior in regards to dietary and supplemental vitamin D intake. The mechanism between high dietary vitamin D and pain remains unclear and warrants further investigation. If a reduction in pain is not the medium through which vitamin supplementation is related to improved function, it opens the door to investigating other aspects of the relationship.

Limitations

There are limitations to acknowledge in the present study. A primary limitation is that our study is an observational study of baseline data. A longitudinal analysis may have provided more information between nutrition, symptom severity, and physical function. In our study, dietary and supplemental vitamin C revealed no correlative effects in patients with symptomatic knee OA; compared to dietary nutrients, the amount of time pharmaceutical nutrients need to be present in a person's system in order to take effect may be longer. In addition, intake of these micronutrients may not be reflective of what is biologically available in the body for it to demonstrate an effect. Utilizing the Brief Block Food Frequency Questionnaire to measure dietary and supplemental intake also limits our study since respondents could over or under-report actual intake of micronutrients. Another consideration would be the quality and purity of the supplements in question. There may be

other factors that may improve physical function such as acupuncture, water-based exercises, and physical therapy. Pain severity may have been influenced by chondroitin, glucosamine, and statin use. Many studies have also gathered biological data to describe the prevalence of vitamin D and C in individuals with or without knee osteoarthritis. Although we understand that biological factors may have a large impact on certain outcomes, the dataset limited further investigation beyond this analyses. Despite the study's limitations and considerations, our study raises additional questions about the role of micronutrients, vitamin D in particular, which may affect management of OA.

Conclusion

Future research should look at the role of current supplemental treatment recommendations, supplements, biological factors, and supportive therapy to better evaluate for other factors associated with symptoms and level of function at different time points in disease progression. Research studies are needed to establish directionality and create a clearer understanding of the relationship between OA and micronutrients from diet and supplementation. Future randomized controlled trials are also needed in order to better understand the relationship between vitamin D and C with physical function and pain in individuals with OA.

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TAKE AWAY POINTS

- Associations of Vitamins C and D with decreasing osteoarthritic pain severity and increasing function are not definitive in individuals with osteoarthritis.
- High levels (271.2IU-1002.3IU) of dietary vitamin D intake were found to be positively associated with pain while high levels of supplemental vitamin D were found to be inversely related to physical function.
- We found no statistical significant associations for the daily intake of vitamin C with physical function or pain.
- Our results suggest that micronutrients are associated with greater knee pain. These findings warrant further investigation, .

Table 1.

Demographic characteristics of participants (n=1373)

Characteristics	n	%	Mean	SD	Median	Range
Age (years)			61.5	9.5	62	45–79
Gender						
Male	592	43.1				
Female	781	56.9				
Ethnicity						
Hispanic/Latino	19	1.4				
Non-Hispanic/Latino	1354	98.6				
Race						
White	970	70.6				
Black	361	26.3				
Asian	11	0.8				
Other Non-white	31	2.3				
BMI (kg/m ²)			30.2	4.9	29.8	18.2–48.7
Comorbidities						
0	947	69.0				
1	248	18.1				
2	108	7.9				
3	41	3.0				
4	7	0.5				
5	2	0.1				
6	3	0.2				
7	1	0.1				
10	1	0.1				
Missing	15	1.1				

Table 2.

Daily nutritional intake of micronutrients

Micronutrient	50th percentile	85th percentile	90th percentile	Mean	SD	Range
Daily vitamin C from supplements (mg)	60	560	931.9	273.3	441.1	0–3810
Daily vitamin C from food (mg)	100.3	176.7	204	113.7	72.63	4.50–654.9
Daily vitamin D from supplements (IU)	200	400	600	237.1	217.5	0–600
Daily vitamin D from food (IU)	104.6	235.7	271.2	136.2	107.4	4.38–1002.3

Table 3.

Associations of vitamins C and D on WOMAC pain and function

Variable	Pain					Function (Disability)				
	n	β	p-value	S.E.	95% CI	n	β	p-value	S.E.	95% CI
Dietary Vitamin C										
>90 th Percentile	137	0.136	0.114	0.281	-0.108-1.004	134	0.088	0.311	0.407	-0.391-1.218
50-90 th Percentile	549	-0.008	0.844	0.146	-0.314-0.257	547	0.004	0.925	0.219	-0.403-0.450
<50 th Percentile	687	-0.069	0.070	0.052	-0.196-0.008	685	-0.095	0.01*	0.076	-0.339-0.040
Supplemental Vitamin C										
>90 th Percentile	137	0.001	0.991	0.195	-0.383-0.387	135	-0.050	0.567	0.281	-0.395-0.718
50-90 th Percentile	416	-0.078	0.112	0.051	-0.182-0.019	416	-0.090	0.065	0.074	-0.282-0.009
<50 th Percentile	820	-0.066	0.059	0.012	-0.047-0.001	815	-0.015	0.662	0.018	-0.044-0.028
Dietary Vitamin D										
>90 th Percentile	137	0.238*	0.005	0.242	0.210-1.166	135	0.192*	0.025	0.344	0.099-1.459
50-90 th Percentile	549	-0.057	0.181	0.104	-0.344-0.065	547	-0.089*	0.038	0.016	-0.648-0.018
<50 th Percentile	687	-0.025	0.511	0.055	-0.143-0.071	682	-0.034	0.375	0.079	-0.225-0.085
Supplemental Vitamin D										
>85 th Percentile	203	-0.136	0.052	0.387	-1.517-0.008	202	0.179*	0.011	0.560	-2.550-0.340
50-85 th Percentile	476	-0.024	0.604	0.269	-0.667-0.388	474	-0.019	0.674	0.391	0.932-0.603
<50 th Percentile	633	0.007	0.853	0.014	-0.026-0.031	630	0.005	0.904	0.021	-0.039-0.044

Note:

*p<0.05

Table 4.

Associations of vitamins C and D on WOMAC pain and function after adjustment for age, sex, race, BMI, and comorbidities.

Variable	Pain			Function (Disability)						
	n	β	p-value	S.E.	95% CI	n	β	p-value	S.E.	95% CI
Dietary Vitamin C										
z<50 th Percentile	674	-0.040	0.297	0.052	-0.158-0.048	672	-0.071	0.066	0.077	-0.068-0.001
Supplemental Vitamin C										
50 th -90 th Percentile						408	-0.072	0.129	0.071	-0.248-0.031
<50 th Percentile	811	-0.016	0.644	0.012	-0.029-0.018					
Dietary Vitamin D										
>90 th Percentile	135	0.180 [*]	0.028	0.233	0.055-0.979	135	0.154	0.067	0.0338	-4.843-3.605
50 th -90 th Percentile						540	-0.067	0.099	0.0893	2.056-5.565
Supplemental Vitamin D										
>85 th Percentile	203	-0.083	0.223	0.378	-1.207-0.283	202	-0.150 [*]	0.028	0.0549	-2.297--0.133

Note:

*p<0.05

Table 5.

WOMAC pain and function (disability) scores

Variable	n	Mean	SD	Median	Minimum	Maximum
Pain						
All	1373	4.25	3.30	3.50	0	19.50
Dietary Vitamin C						
>90th Percentile	137	5.41	3.92	5.00	0	18.50
50–90th Percentile	549	3.91	3.05	3.00	0	18.00
<50th Percentile	687	4.29	3.31	3.50	0	19.50
Supplemental Vitamin C						
>90th Percentile	137	3.67	2.95	3.00	0	13.00
50–90th Percentile	416	4.17	3.22	3.50	0	16.50
<50th Percentile	820	4.39	3.39	3.50	0	19.50
Dietary Vitamin D						
>90th Percentile	137	4.07	3.39	3.50	0	16.50
50–90th Percentile	549	4.19	3.17	3.50	0	18.00
<50th Percentile	687	4.34	3.39	3.50	0	19.50
Supplemental Vitamin D						
>85th Percentile	602	3.98	3.10	3.00	0	16.50
50–85th Percentile	128	4.22	3.23	3.44	0	14.00
<50th Percentile	633	4.50	3.48	4.00	0	19.50
Function (Disability)						
All	1366	14.31	11.55	11.54	0	67.47
Dietary Vitamin C						
>90th Percentile	134	18.75	13.66	17.50	0	63.50
50–90th Percentile	547	13.09	10.67	10.50	0	50.00
<50th Percentile	685	14.43	11.58	11.54	0	67.47
Supplemental Vitamin C						
>90th Percentile	135	12.34	9.97	10.00	0	42.50
50–90th Percentile	416	14.60	11.40	11.67	0	62.50
<50th Percentile	815	14.50	11.86	12.00	0	67.47
Dietary Vitamin D						
>90th Percentile	137	13.73	11.10	11.50	0	62.50
50–90th Percentile	547	13.86	13.86	11.50	0	59.50
<50th Percentile	682	14.81	12.02	12.00	0	67.47
Supplemental Vitamin D						
>85th Percentile	599	13.69	11.01	11.00	0	62.50
50–85th Percentile	127	14.15	14.15	12.00	0	48.17
<50th Percentile	630	14.88	12.16	12.00	0	67.47