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Vitamin D Intake Is Inversely Associated With Rheumatoid Arthritis

Results From the Iowa Women's Health Study

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Objective. **Vitamin D is a potent regulator of calcium homeostasis and may have immunomodulatory effects. The influence of vitamin D on human autoimmune disease has not been well defined. The purpose of this study was to evaluate the association of dietary and supplemental vitamin D intake with rheumatoid arthritis (RA) incidence.**

Methods. **We analyzed data from a prospective cohort study of 29,368 women of ages 55–69 years without a history of RA at study baseline in 1986. Diet was ascertained using a self-administered, 127-item validated food frequency questionnaire that included supplemental vitamin D use. Risk ratios (RRs) and 95% confidence intervals (95% CIs) were estimated using Cox proportional hazards regression, adjusting for potential confounders.**

Results. **Through 11 years of followup, 152 cases of RA were validated against medical records. Greater intake (highest versus lowest tertile) of vitamin D was inversely associated with risk of RA (RR 0.67, 95% CI 0.44–1.00, *P* for trend = 0.05). Inverse associations were apparent for both dietary (RR 0.72, 95% CI 0.46–1.14, *P* for trend = 0.16) and supplemental (RR 0.66, 95% CI 0.43–1.00, *P* for trend = 0.03) vitamin D. No individual food item high in vitamin D content and/or calcium was strongly associated with RA risk, but a composite measure of milk products was suggestive of an inverse association with risk of RA (RR 0.66, 95% CI 0.42–1.01, *P* for trend = 0.06).**

Conclusion. **Greater intake of vitamin D may be associated with a lower risk of RA in older women, although this finding is hypothesis generating.**

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology in which both genetic and nongenetic factors contribute to disease susceptibility (1). Vitamin D plays an important role in bone metabolism and may also have immunomodulatory effects (2). Vitamin D has been shown to suppress the development of autoimmunity in some experimental animal models, but its effects on the human immune system are more speculative (3). Few studies have examined dietary or nutritional intake prior to RA onset, and none have assessed the association of vitamin D with disease onset. The purpose of this study was to evaluate the association of vitamin D intake with incident RA utilizing a population-based prospective cohort. Due to its strong relationship with vitamin D, we secondarily examined the association of calcium consumption with RA onset.

SUBJECTS AND METHODS

Study cohort. The Iowa Women's Health Study (IWHS) is a population-based prospective cohort study initiated in 1986 enrolling 41,836 women of ages 55–69 years who responded to a detailed self-administered questionnaire. Details of the IWHS cohort design (4) and of the RA case

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Table 1. Demographics at the baseline survey and clinical characteristics of subjects with or without rheumatoid arthritis (RA), Iowa Women's Health Study, 1986–1997*

	Subjects		
	With RA (n = 152)	Without RA (n = 29,368)	*P*
Age, mean ± SD years	61.1 ± 3.9	61.5 ± 4.2	0.23
Body mass index, mean ± SD kg/m^2	26.8 ± 4.6	26.8 ± 4.9	0.84
Vitamin D intake, IU/day, median (IQR)			
Food and supplements	272.5 (338.7)	336.0 (377.9)	0.06
Food only	206.6 (193.6)	221.1 (193.8)	0.34
Supplements only	0 (200)	0 (400)	0.10
Marital status, %			
Currently married	84.9	78.7	
Separated/divorced	4.6	4.1	0.07
Widowed	7.9	14.8	
Never married	2.6	2.5	
Hormone replacement therapy, %			
Never used	55.3	61.0	
Formerly used	34.9	27.3	0.11
Currently use	9.9	11.6	
Smoking status, %			
Never smoked	58.4	66.7	
Former smoker	20.1	19.6	0.005
Current smoker	21.8	13.7	
Decaffeinated coffee, cups/day, %			
None	36.8	42.7	
1–2.5	28.3	31.6	0.02
≥2.6	34.9	25.7	
Age at RA onset, mean ± SD years	67.8 ± 4.9	–	
Average time from RA onset to diagnosis, mean ± SD months	13.4 ± 21.7	–	
ACR RA criteria (16) satisfied, mean ± SD	4.6 ± 1.1	–	

* IQR = interquartile range; ACR = American College of Rheumatology (formerly, the American Rheumatism Association).

identification and validation process have been previously reported (5–7). The baseline (1986) questionnaire included demographic data, medical and reproductive history, lifestyle factors, and a 127-item semiquantitative food frequency questionnaire that included supplement use. All subjects provided informed consent, and the study was approved by the University of Iowa Institutional Review Board.

Calcium and vitamin D assessment. Vitamin D and calcium intake were obtained from the respondents' responses to the baseline food frequency questionnaire. The questionnaire asked how often, on average, during the past year the respondents had consumed a specified portion size or unit of food. There were 9 possible responses ranging from "never or less than once per month" to "6 or more times per day." The daily intakes of both vitamin D and calcium were calculated by multiplying the frequency of consumption of each unit of food by the calcium or vitamin D content of the specified portions, using a database provided by Willett and colleagues (8). These values were based on information from the US Department of Agriculture. Additionally, information was obtained on the use of multivitamins (brand name, frequency of use) and on the use of supplements containing only vitamin D or only calcium (including range of dose on a daily basis). Data on duration of supplement use were not collected. Multivitamin brands were coded individually for estimation of intake of vitamins and minerals from supplements.

Data analysis. The at-risk cohort consisted of 29,368 women obtained from the 35,635 women who responded to the 1992 and/or 1997 surveys. Exclusion criteria included RA diagnosis before 1987 (n = 2,102; no attempt at validation); participation in the validation survey (i.e., potentially incident cases), but not meeting the validation criteria (n = 2,197); and leaving 30 or more food items blank on the questionnaire or having implausible daily energy intakes (i.e., <600 kcal or ≥5,000 kcal; n = 1,968 including 6 incident cases). Person-years of followup accumulated from the date of receipt of the 1986 baseline questionnaire to either the date of RA symptom onset or September 30, 1992 (date of followup 3 questionnaire) for women who did not complete the followup 4 questionnaire or August 31, 1997 (date of followup 4 questionnaire) for all remaining women.

Dietary variables were categorized into tertiles based on the distribution of their consumption among all women included in the analysis. A composite score of servings of all milk products comprised skim milk, whole milk, ice milk, ice cream, yogurt, cottage cheese, cream cheese, and other cheeses. Relative risks (RRs) and 95% confidence intervals (95% CIs) were calculated as the measure of association

Table 2. Relative risks (RRs) and 95% confidence intervals (95% CIs) for risk of rheumatoid arthritis according to intake of vitamin D from food and supplements, Iowa Women's Health Study, 1986–1997

Vitamin D measure, IU/day*	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)†
Total				
<221.4	64	103,613	1.00 (referent)	1.00 (referent)
221.4–467.6	42	103,741	0.64 (0.43–0.97)	0.67 (0.45–1.01)
≥467.7	46	106,827	0.67 (0.45–1.00)	0.67 (0.44–1.00)
P for trend			0.05	0.05
Dietary				
<169	59	103,586	1.00 (referent)	1.00 (referent)
169–289.9	50	103,750	0.81 (0.55–1.21)	0.87 (0.58–1.29)
≥290	43	106,845	0.68 (0.44–1.06)	0.72 (0.46–1.14)
P for trend			0.09	0.16
Supplemental				
Nonusers	109	200,008	1.00 (referent)	1.00 (referent)
<400	13	37,423	0.64 (0.36–1.14)	0.65 (0.36–1.15)
≥400	30	76,750	0.69 (0.46–1.04)	0.66 (0.43–1.00)
P for trend			0.05	0.03

* Tertiles of standard supplemental dose.
† Adjusted for age, caloric intake, smoking status, hormone replacement therapy, decaffeinated coffee consumption, and β-cryptoxanthin intake.

between the dietary factor of interest and RA incidence and were estimated using Cox proportional hazards regression (9). Models were initially adjusted for age and total energy (continuous covariates) in the Cox model. Total energy was included in all models to adjust for systematic over- and under-reporting of food intake (10). Multivariable models were adjusted for age, total energy, and factors that have been associated with RA in this cohort (5–7). These factors included smoking history (never, former, current), hormone replacement therapy (never, former, current), consumption of β-cryptoxanthin (<40 μg/day, 40–86.9 μg/day, ≥87 μg/day), and decaffeinated coffee consumption (none, 1–2.5 cups/day, ≥2.6 cups/day). Pearson correlation coefficients were computed to assess the relationship between vitamin D and calcium intake from food, supplements, and total intake.

RESULTS

Through 11 years (314,181 person-years) of followup, 152 cases of RA were validated. Demographic and clinical characteristics are presented in Table 1. The mean age of RA patients at the baseline survey was 61.1 years with a mean age at RA onset of 67.8 years. A majority (>78%) of the cohort was married at baseline, and the mean body mass index was 26.8 kg/m^2. The mean time to diagnosis from RA symptom onset was ~1 year (mean 13.4 months). Factors that may be indicative of poor health practices (education, employment status at baseline, place of residence at baseline, occupation at baseline, physical activity at baseline) did not show any differences between cases and noncases across levels of total vitamin D intake and were not associated with RA risk in this cohort.

There was a strong correlation between vitamin D intake from food only and calcium intake from food only (r = 0.84). The strongest correlation between vitamin D and calcium intake derived from individual food items was that with skim milk. The correlation between total vitamin D intake and total calcium intake was moderate (r = 0.54). The association between vitamin D intake from food and risk of RA did not vary by the level of calcium consumption from food, nor did the association between total vitamin D intake and risk of RA vary by level of total calcium consumption. Therefore, no effect modification was seen.

The associations of RA with vitamin D intake from both diet and supplement use are presented in Table 2. Greater intake (highest versus lowest tertile) of total daily vitamin D was inversely associated with risk of RA (RR 0.67, 95% CI 0.44–1.00, *P* for trend = 0.05). Inverse associations were apparent for both dietary (RR 0.72, 95% CI 0.46–1.14, *P* for trend = 0.16) and supplemental (RR 0.66, 95% CI 0.43–1.00, *P* for trend = 0.03) vitamin D. These measures of effect remained robust after adjustment for multiple confounders.

Total calcium intake from all sources was not associated with risk of RA (data not shown). However, calcium from dietary sources was suggestive of an inverse trend (RR 0.69, 95% CI 0.44–1.10, *P* for trend =

Table 3. RRs and 95% CIs for risk of rheumatoid arthritis according to intake of vitamin D and calcium-containing dairy products, Iowa Women's Health Study, 1986–1997*

Dairy product, servings/month	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)†
Milk products‡				
1–35	58	98,352	1.00 (referent)	1.00 (referent)
36–67	52	107,109	0.80 (0.54–1.17)	0.80 (0.54–1.18)
≥68	42	108,720	0.63 (0.41–0.98)	0.66 (0.42–1.01)
P for trend			0.04	0.06
Butter				
None	115	217,020	1.00 (referent)	1.00 (referent)
≥1	37	97,161	0.70 (0.48–1.02)	0.72 (0.49–1.06)
Margarine				
None	23	36,462	1.00 (referent)	1.00 (referent)
1–21	24	66,612	0.58 (0.33–1.04)	0.56 (0.31–1.02)
22–74	46	104,300	0.73 (0.44–1.22)	0.71 (0.43–1.19)
≥75	59	106,807	0.96 (0.58–1.58)	0.92 (0.56–1.52)
P for trend			0.49	0.58
Skim milk				
None	40	73,802	1.00 (referent)	1.00 (referent)
1–3	11	16,334	1.23 (0.63–2.40)	1.23 (0.63–2.40)
4–29	34	74,235	0.84 (0.53–1.33)	0.85 (0.53–1.36)
≥30	67	149,810	0.82 (0.55–1.21)	0.87 (0.58–1.30)
P for trend			0.24	0.39
Whole milk				
None	122	253,034	1.00 (referent)	1.00 (referent)
≥1	30	61,147	1.04 (0.70–1.56)	1.04 (0.69–1.57)

* See Table 2 for definitions.
† Adjusted for age, caloric intake, smoking status, hormone replacement therapy, decaffeinated coffee consumption, and β-cryptoxanthin intake.
‡ Comprising skim milk, whole milk, ice milk, ice cream, yogurt, cottage cheese, cream cheese, and other cheeses.

0.11) for the highest tertile of dietary calcium intake relative to the lowest. However, this association disappeared ($P = 0.50$) when total vitamin D intake was included in the model. No RA association was seen with supplemental calcium use.

Relationships of individual food items containing vitamin D and/or calcium with the risk of RA are presented in Table 3. No individual food item high in vitamin D content and/or calcium was strongly associated with RA risk. A composite score of servings of milk products combined was inversely associated with risk of RA (RR 0.66, 95% CI 0.42–1.01, P for trend = 0.06). This association persisted even when supplemental vitamin D intake was included in the model.

There was a suggestion of interaction between vitamin D and smoking ($P = 0.17$) (data not shown). For smokers with high vitamin D intake, there was a trend toward an inverse association with RA (RR 0.66, 95% CI 0.32–1.22), whereas smokers with low vitamin D intake were at increased risk for RA (RR 1.8, 95% CI 1.16–2.75) (both comparisons relative to nonsmokers with low vitamin D intake).

DISCUSSION

In this prospective cohort study of older women, we found an inverse association between greater intake of vitamin D and RA risk. The association persisted even after potentially confounding variables were included in the analyses. Vitamin D from supplements showed a stronger inverse association with RA development than did dietary vitamin D. No individual food item high in calcium or vitamin D was associated with RA. Lower serum levels of vitamin D and dietary intake of vitamin D in smokers have been reported by investigators in several studies (11). Since smoking may deplete vitamin D, we evaluated this possibility and found a suggestive interaction between smoking and vitamin D, although this was an exploratory analysis.

Vitamin D has immunologic activity independent of its crucial role in calcium regulation (12). Animal models of autoimmune disease have shown beneficial effects of vitamin D as an immunosuppressant. For example, murine models of human RA demonstrated both decreased incidence and severity of disease in mice

treated with active vitamin D (3). Evidence supporting an effect of vitamin D in RA specifically also is derived from clinical observations. Manolagas et al found that a significantly greater proportion of seropositive RA patients (76%) had lymphocytes possessing vitamin D receptors compared with controls (18%) (13). Within the rheumatoid joint, the active form of vitamin D has been shown to be synthesized in RA synovium and is thought to be stimulated by interleukin-1 (IL-1) and/or IL-2 (14). Locally produced vitamin D may act in a paracrine manner to decrease T cell responsiveness through the inhibition of cellular proliferation and reduction in lymphokine production when confronted by an inappropriate and overly exuberant immune response (15).

Since high calcium levels exert negative feedback on the synthesis and action of vitamin D, we examined effects of calcium as well. In our study, the high correlation between calcium and vitamin D from food and the only moderate correlation of total calcium intake with total vitamin D intake, which included supplemental vitamin D, may have been due to vitamin D fortification of calcium-containing foods. Our results did not show an effect modification by calcium and vitamin D intake on the incidence of RA. Calcium from food sources, which was strongly correlated with vitamin D from food sources, appeared to be inversely associated with RA. However, this association was no longer significant when vitamin D was included in the model, suggesting a greater effect of vitamin D.

The strengths of this study include its population-based prospective design and rigorous case validation. This study utilized a validated food frequency questionnaire, although consumption was assessed only at baseline. In many dietary studies, low vitamin levels may be the result of dietary changes due to the disease and/or treatment effects themselves. However, in this cohort, dietary assessment occurred before disease onset.

In addition to its strengths, there are limitations to this study. Subjects were not clinically examined and some may have been misclassified, which is less of a concern in this study due to the large comparison group. Additionally, older adults, such as the women in the IWHS, tend to have low levels of vitamin D intake, which may have influenced our results. However, this effect would presumably be nondifferential between RA and non-RA cases and, if anything, would create a bias toward the null hypothesis. A potentially important source of vitamin D is from sun exposure, which was not measured in this study. Since sunlight exposure substantially affects vitamin D levels, this might represent a source of unmeasured confounding. Although the participation of mainly elderly white women from the state of Iowa should not influence the validity of our findings, it may limit their generalizability. Finally, our findings were not based on an a priori hypothesis; it is therefore possible that chance alone explains these results. However, there is a compelling biologic explanation for these findings.

In summary, greater intake of vitamin D showed an inverse association with incident RA in this cohort of elderly women. While the immunomodulatory effects of vitamin D are not yet fully elucidated, the results from this study suggest a possible role for vitamin D in reducing the risk of an immunologic disorder. These results are largely hypothesis generating; further studies will be required to corroborate or refute our findings.

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