Prevalence of Vitamin D Insufficiency/Deficiency in Rheumatoid Arthritis and Associations with Disease Severity and Activity

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ABSTRACT. ***Objective.*** 25-hydroxy-vitamin D (25-OH-D) insufficiency/deficiency is increasingly prevalent and has been associated with many chronic diseases, including rheumatoid arthritis (RA). Our purpose was to define the prevalence and associations of 25-OH-D insufficiency/deficiency in a cohort of US veterans with RA.

Methods. Vitamin D status (25-OH-D) was assessed in patients with RA using radioimmunoassay on banked plasma collected at enrollment. Insufficiency was defined as concentrations < 30 ng/ml and deficiency as < 20 ng/ml. Associations of 25-OH-D insufficiency/deficiency with patient characteristics obtained at enrollment were examined using multivariate logistic regression, adjusting for age, sex, season of enrollment, and race.

Results. Patients (850 men, 76% Caucasian) had a mean (SD) age of 64 (SD 11.3) years. The prevalences of 25-OH-D insufficiency and deficiency were 84% and 43%, respectively. After multivariate adjustment, both insufficiency and deficiency were more common with anti-cyclic citrullinated peptide antibody positivity and non-Caucasian race, and in the absence of vitamin D supplementation. 25-OH-D deficiency, but not insufficiency, was independently associated with higher tender joint counts and highly sensitive C-reactive protein levels.

Conclusion. In a predominantly elderly, male RA population, 25-OH-D insufficiency was highly prevalent. With the increasing adverse health outcomes associated with hypovitaminosis D, screening and supplementation, particularly among minority, seropositive patients with RA, should be performed routinely. (J Rheumatol First Release Oct 15 2010; doi:10.3899/jrheum.100516)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
ANTI-CYCLIC CITRULLINATED PEPTIDE
25-HYDROXYL-VITAMIN D
US VETERANS

There is a plethora of data regarding the growing epidemic of hypovitaminosis D in the US and elsewhere, with increased attention to its many potential noncalcitropic effects, separate from its known associations with increased fracture risk[1,2,3,4]. For instance, vitamin D has been shown to alter the expression of more than 200 genes that affect an array of cellular functions including proliferation, differentiation, apoptosis, and angiogenesis[5]. Such immune interactions have furthered the understanding of the associations of vitamin D with various cancers[6,7,8,9]. Data indicate sufficient vitamin D levels have a protective role against colon cancer, but are less supportive in showing prevention of malignancies of the prostate, breast, and pancreas. 25-hydroxy-vitamin D (25-OH-D) has been reported to inhibit T cell expansion and downregulate select chemokines and cytokines, inflammatory mediators that are targeted in the management of inflammatory rheumatic diseases such as rheumatoid arthritis (RA).

Although not found in all studies, low vitamin D intake has been implicated as a risk factor in development of RA, and recent investigations have linked low vitamin D levels with increased disease activity and severity in patients with inflammatory arthritis[10,11,12,13,14]. In addition to its potential immunomodulatory and antiinflammatory effects, vitamin

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The Veterans Affairs Rheumatoid Arthritis Registry (VARA) receives grant support from NIH/NIAMS (R03 AR054539), the Health Services Research and Development (HSR&D) Program of the Veterans Affairs; and supported by unrestricted research funds from Abbott Laboratories and Bristol-Myers Squibb.

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Accepted for publication August 4, 2010.

D insufficiency has been associated with the incidence of other chronic diseases including diabetes, malignancy, and heart disease, in addition to increased all-cause mortality[15,16,17,18,19,20].

Inadequate vitamin D has been particularly recognized as a major health problem among US veterans that receive care from the Veterans Affairs Health Administration (VHA). In a recent study of more than 2000 longterm care veterans, only 10% were screened for vitamin D status, more than half had inadequate serum concentrations, and only 13% of these received appropriate vitamin D supplementation as assessed 3 months later by repeat vitamin D measurements[21]. The VHA is the single largest integrated health system in the US, serving some 5 million veterans, a population that is rapidly aging, racially diverse, and with substantial comorbid illnesses. Hence, VA patients may be disproportionately vulnerable to the incidence and effects of low vitamin D. Risk factors for vitamin D insufficiency, including older age[1], non-Caucasian race[1,2], obesity, and cigarette smoking[22,23], are all highly prevalent in the VA population.

In light of the increased prevalence of hypovitaminosis D in the US and the reported associations with risk for and disease progression of RA, we examined the prevalence of vitamin D insufficiency/deficiency and its associations among US veterans with RA.

MATERIALS AND METHODS

Participants. Patients were enrollees of the VA Rheumatoid Arthritis (VARA) Registry[24]. In brief, VARA is a prospective longitudinal database enrolling patients that meet American College of Rheumatology (ACR) classification criteria[25] for RA and who receive care at one of 9 participating VA sites. Baseline clinical data and banked serum/plasma samples are obtained at enrollment. VARA has received Institutional Review Board approval at all sites, and all study participants provided written informed consent.

Patient characteristics, including self-reported race, sex, age, body mass index (BMI, kg/m^2), smoking history (current, past, never), and education level (high school, other) were recorded. Comorbidity was accounted for by a cumulative score of cardiovascular disease, diabetes, hypertension, hyperlipidemia, chronic kidney disease, chronic obstructive pulmonary disease, interstitial lung disease, and depression (range 0–8). The number of deaths, from any cause, was also recorded. Vital status was ascertained using a combination of next-of-kin report and electronic medical record review. Season of enrollment was documented as follows: summer, June 21 to September 20; fall, September 21 to December 20; winter, December 21 to March 20; and spring, March 21 to June 20.

25-OH-D measurement. Banked plasma samples from VARA patients collected at enrollment were available for 25-OH-D measurement, using a commercial radioimmunoassay (RIA; DiaSorin, Saluggia, Vercelli, Italy). 25-OH-D was measured rather than other vitamin D metabolites (i.e., 1,25-OH-D), as 25-OH-D is independent of calcium and phosphate status (measurements not routinely available) and to allow comparisons with existing data in RA patients and general populations. 25-OH-D insufficiency was defined as < 30 ng/ml (< 70 nmol/l), and deficiency as < 20 ng/ml (< 50 nmol/l)[26,27].

Measures of RA disease severity and activity. Assessments of RA disease severity and activity were also collected at time of 25-OH-D measurement, and included the Multi-Dimensional Health Assessment Questionnaire (MD-HAQ, range 0–3)[28], rheumatoid factor [RF; measured by nephelometry (Siemens), positive values ≥ 15 IU/ml], and anti-cyclic citrullinated peptide antibody [anti-CCP antibody, measured using second-generation ELISA (Diastat; Axis-Shield Diagnostics, Dundee, Scotland), positive values ≥ 5 U/ml]. Hand radiographs were available to determine presence or absence of erosions or periarticular osteopenia, consistent with ACR criteria[25]. Measurements of RA disease activity included pain scores (range 0–10), patient global well-being scores (visual analog scale 0–100 mm), tender and swollen joint counts (TJC, SJC, 0 to 28 joints), high-sensitivity C-reactive protein (hs-CRP; normal < 3 mg/l), and erythrocyte sedimentation rate (ESR; normal < 25 mm/h). Disease activity score [DAS28 (4v), ESR][29] was calculated at the time of enrollment.

Medications. Disease modifying antirheumatic drug (DMARD) use was recorded at baseline, and included methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, auranofin, parenteral gold, cyclosporine, and biologic response-modifying agents (etanercept, infliximab, adalimumab, abatacept, rituximab, or anakinra). Data on glucocorticoid use and nonsteroidal antiinflammatory agents were also available. Vitamin D supplementation was identified from the VARA database and through linkage to pharmacy dispensing data from the VA Pharmacy Benefits Management database (PBM; HINES VAMC, and Chicago, IL). Patients were defined as using vitamin D supplementation if they reported over the counter use of vitamin D at the time of enrollment (VARA database) or if they had a prescription dispensed for vitamin D, cholecalciferol and/or calcium plus vitamin D within the 90 day period preceding enrollment (PBM data). Data specific to the daily dose of vitamin D supplement taken were not routinely available.

Statistical analysis. All analyses were performed using Stata v10.1 (Stata, College Station, TX, USA). The prevalence of 25-OH-D insufficiency and deficiency and corresponding 95% confidence intervals (CI) were calculated using the Stata command "proportion." Descriptive analyses (chi-square and Student t test) were performed to compare frequencies and means of variables in individuals with vitamin D insufficiency versus those with sufficient vitamin D concentrations. Associations of the patient factors with vitamin D insufficiency and deficiency were examined using multivariate logistic regression, with all analyses adjusted for age, sex, season, and race (Caucasian vs non-Caucasian). Additional variables with p values < 0.10 after adjustment for age, sex, season, and race were entered into subsequent multivariate models, with backwards stepwise elimination until all remaining variables met the significance threshold ($p < 0.05$). Variables examined as possible determinants of vitamin D status included age, sex, race, education, smoking status, season of enrollment, medications (glucocorticoids, DMARD, biologic DMARD), and vitamin D supplementation within 90 days of enrollment. Other variables examined included nodules, the presence of radiographic damage, RF/anti-CCP positivity, pain, MD-HAQ score, joint counts, patient global assessment, ESR, DAS28, hs-CRP, BMI, and comorbidity count. All analyses accounted for clustering by study site.

RESULTS

Patient characteristics. Six participating VA sites (Dallas, TX; Denver, CO; Jackson, MI; Omaha, NE; Salt Lake City, UT; and Washington, DC) contributed to the registry for this analysis (Figure 1). Patients from 3 VA sites recently added to the VARA Registry did not contribute samples to the VARA cohort until after 25-OH-D measurements were completed and were excluded from this analysis. There were 1181 patients enrolled in VARA with vitamin D values available for the analysis. There were 320 participants for whom PBM data were not available because they were enrolled after the linkage with this dataset and they were excluded from the analysis. An additional 11 subjects with missing clinical data within 90 days of enrollment were also

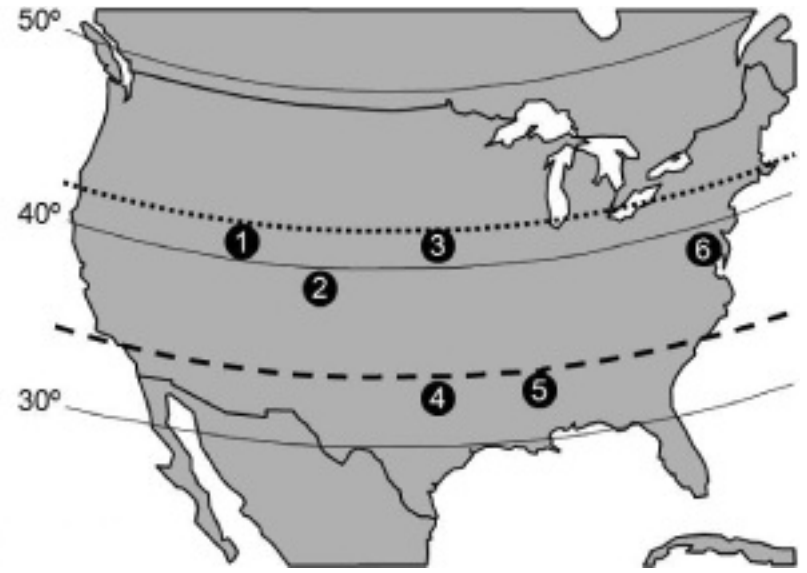

Figure 1. Latitudes of study sites. 1: Salt Lake City, UT; 2: Denver, CO; 3: Omaha, NE; 4: Dallas, TX; 5: Jackson, MI; 6: Washington, DC. Area above the dashed line and below the dotted line has insufficient sun exposure for cutaneous vitamin D synthesis from November through February[23]. Area below dashed line allows for cutaneous production of vitamin D throughout the year[28].

excluded, leaving 850 evaluable patients for further analyses. Those with missing PBM data (n = 320) were similar to the remaining subjects with respect to sex (p = 0.89) and 25-OH-D concentrations (p = 0.16), but were more likely to be Caucasian (p = 0.012).

Baseline sociodemographic and disease-specific characteristics of all study participants (and patients with vitamin D insufficiency vs sufficiency) are shown in Table 1. Ninety percent of study participants were men, with mean disease duration 12.4 years (SD 11.5) and a mean age of 64 years (SD 11.3). The majority of patients were Caucasian (76%), and African Americans comprised the majority of the non-Caucasian population (17% of total). A majority of study participants were current or former smokers (80%) and had received at least a high school education (83%). The mean BMI was 27.9 kg/m^2 (SD 5.7) and the mean comorbidity count (range 0 to 8) was 2.0 (SD 1.4).

Measures of RA disease severity and activity. A majority of subjects were seropositive for anti-CCP antibody (76%) or RF (81%). Study participants had established disease, with moderate disease activity mean DAS28 of 4.1 (SD 1.6), moderate functional limitation with mean MD-HAQ of 1.0 (SD 0.6), and roughly one-third were receiving biologic therapy. There was elevation of both inflammatory markers measured: hs-CRP was markedly elevated, 13.2 mg/l (SD 19.5), whereas ESR was mildly abnormal, 27.7 mm/h (SD 23.6).

Vitamin D status. The mean 25-OH-D concentration was 22.7 ng/ml (SD 10.8) and about one-third (34%) of patients were receiving vitamin D supplementation. The overall frequency of vitamin D insufficiency/deficiency is shown in Figure 2, along with frequencies for patient subgroups based on sex, race, and autoantibody status. The overall prevalence of 25-OH-D insufficiency (< 30 ng/ml) was 84% (95% CI 82%–87%) with a prevalence of vitamin D deficiency (< 20 ng/ml) of 42% (95% CI 40%–46%). In unadjusted analyses, vitamin D insufficiency was more common with younger age, non-Caucasian race, higher BMI, anti-CCP antibody positivity, and the absence of vitamin D supplementation (Table 1).

Results from multivariate analyses are shown in Table 2. Factors independently associated with lower risk of 25-OH-D insufficiency (< 30 ng/ml) included Caucasian race (vs non-Caucasian) and the use of vitamin D supplementation. Anti-CCP antibody positivity was associated with an approximate 2-fold increased risk of 25-OH-D insufficiency. Factors associated with a higher risk of vitamin D deficiency (< 20 ng/ml) included spring enrollment (vs winter), a lack of vitamin D supplementation, anti-CCP antibody positivity, and higher hs-CRP concentrations and tender joint counts (Table 2). There was no association between vitamin D status and site of enrollment (data not shown).

DISCUSSION

In a cohort of US veterans with RA, the overall prevalence of 25-OH-D insufficiency was 84%, and a 25-OH-D level below 20 ng/ml (i.e., deficiency) was found in almost half (45%). Comparisons of 25-OH-D measurements across

Table 1. Patient characteristics among US veterans with RA: total study population and presence/absence of 25 (OH)-vitamin D insufficiency (< 30 ng/ml; 75 nmol/l); data are percentage or mean (SD).

Characteristic	Total RA Population, n = 850	With Vitamin D Insufficiency, n = 715	Without Vitamin D Insufficiency, n = 135	p
Sociodemographic and health measures				
Age, yrs	64.0 (11.3)	63.6 (11.2)	66.3 (11.4)	0.009
Caucasian race/ethnicity	76	74	84	0.017
Men	90	90	93	0.201
High school education or greater	83	82	86	0.338
Ever smoking	80	81	77	0.328
Body Mass Index, kg/m^2	27.9 (5.7)	28.1 (5.8)	26.6 (5.2)	0.006
Comorbidity count (0–8)	2.0 (1.4)	2.0 (1.4)	1.8 (1.3)	0.187
Season of enrollment				
Summer	24	23	27	0.775
Fall	20	20	19	
Winter	25	25	24	
Spring	31	31	30	
RA-related measures				
Anti-CCP antibody-positive, %	76	78	67	0.009
RF-positive, %	81	81	78	0.388
Nodules, %	39	39	36	0.511
Radiographic changes, %	53	53	52	0.852
Pain (0–10)	4.8 (3.0)	4.8 (3.0)	4.6 (3.0)	0.412
MD-HAQ (0–3)	1.0 (0.6)	1.0 (0.6)	1.0 (0.6)	0.698
Tender joint count (0–28)	5.6 (7.1)	5.7 (7.2)	4.8 (6.4)	0.186
Swollen joint count (0–28)	4.5 (5.6)	4.5 (5.7)	4.4 (5.1)	0.923
Disease Activity Score-28	4.1 (1.6)	4.1 (1.6)	4.1 (1.5)	0.999
Patient global well-being (0–100mm)	44.6 (26.7)	44.5 (26.8)	45.1 (26.3)	0.814
hs-CRP, mg/l	13.2 (19.5)	13.1 (19.9)	13.5 (17.7)	0.840
ESR, mm/h	27.7 (23.6)	27.9 (24.0)	26.9 (21.4)	0.660
Duration of RA at enrollment, yrs	12.4 (11.5)	12.4 (11.6)	12.9 (11.2)	0.660
Medication use, %				
DMARD	90	90	92	0.453
Methotrexate	54	54	57	0.462
Biologic	32	30	35	0.352
Prednisone	48	48	47	0.903
Vitamin D supplementation*	34	32	47	< 0.001

* Vitamin D use included vitamin D supplements (2.3%), cholecalciferol (0.5%), combination of calcium and vitamin D supplements (24.2%), or patient-reported supplementation from VARA database (16.3%). Anti-CCP: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; MD-HAQ: Multidimensional Health Assessment Questionnaire; hs-CRP: high sensitivity C-reactive protein; ESR: erythrocyte sedimentation rate; DMARD: disease modifying antirheumatic drugs.

studies are challenging due to variations in the laboratory techniques employed and 25-OH-D cutoff values used to define insufficiency/deficiency. Recognizing this limitation, the prevalence of vitamin D insufficiency in our cohort appears to be greater than that reported in a study of over 2000 institutionalized veterans, where only half had insufficient levels of 25-OH-D[21]. Our results also support the epidemic of low 25-OH-D concentrations in the US, with reports that show a 2 to 6 ng/ml decline in mean circulating concentrations compared to earlier datasets, even after adjusting for differences in age and changes in laboratory techniques[1,2]. In the most recent NHANES analysis (2000 to 2004), 25-OH-D concentrations had decreased in men to a mean level of 24 ng/ml. The mean 25-OH-D level in our predominantly male cohort was similar to that reported in an elderly male cohort of patients with osteoarthritis of the hip[30]. However, whereas previous population analyses (NHANES III) found older individuals had lower 25-OH-D levels, in our RA cohort, younger rather than older patients had lower 25-OH-D concentrations.

Patients with RA who received vitamin D supplementation were less often 25-OH-D insufficient, and our results may suggest a lack of sensitivity among healthcare providers in providing vitamin D supplementation to younger RA patients. Low 25-OH-D levels, particularly deficient levels, were substantially more common among those reporting non-Caucasian race/ethnicity, which in our cohort included primarily African Americans. Data, again from population-based studies, document non-Hispanic blacks, particularly women, to be at much greater risk for

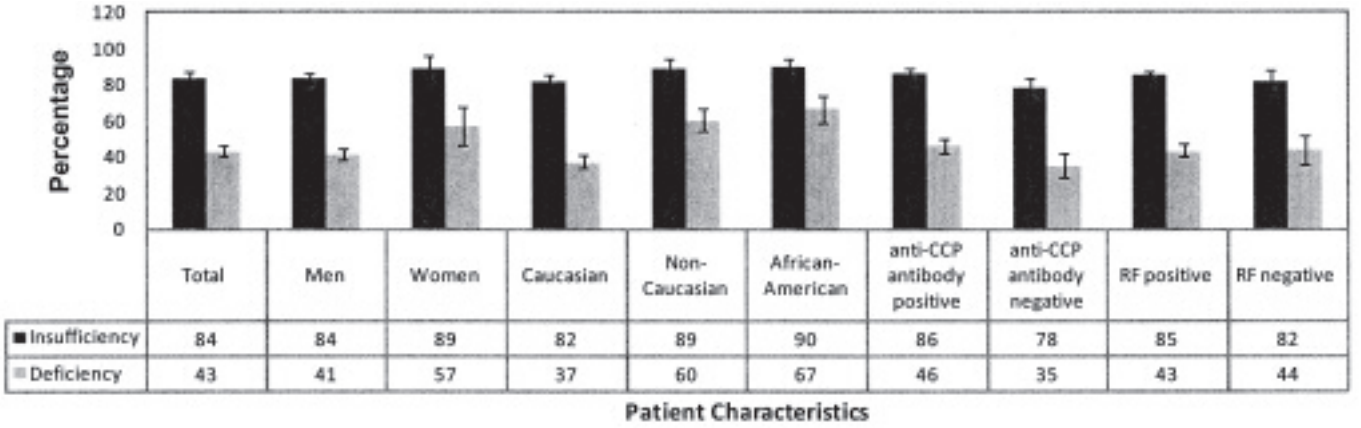

Figure 2. Proportions of patients with RA with 25(OH) vitamin D insufficiency and deficiency (showing 95% confidence intervals), by patients' characteristics.

Table 2. Multivariate associations of patient characteristics with the presence of 25 (OH) vitamin D insufficiency and deficiency in US veterans with rheumatoid arthritis. Associations examined using backwards stepwise regression with age, sex, season, and race/ethnicity forced into the model; variables with p value < 0.1 entered and p value < 0.05 required to remain in final model; variables entered and then removed from model for vitamin D sufficiency included RF positivity and comorbidity count; variables entered and then removed from model examining vitamin D deficiency included swollen joint count and smoking status.

Characteristic	Insufficiency OR (95% CI)	p	Deficiency OR (95% CI)	p
Age, yrs	0.99 (0.98 to 1.00)	0.141	0.99 (0.98 to 1.00)	0.140
Male sex	0.95 (0.63 to 1.43)	0.820	0.80 (0.56 to 1.13)	0.207
Season				
Winter	Referent	—	Referent	—
Summer	0.83 (0.63 to 1.10)	0.187	0.83 (0.67 to 1.03)	0.084
Fall	0.89 (0.46 to 1.72)	0.731	0.80 (0.40 to 1.64)	0.548
Spring	1.00 (0.75 to 1.33)	0.998	1.28 (1.06 to 1.55)	0.011
Caucasian race/ethnicity	0.62 (0.46 to 0.84)	0.002	0.41 (0.33 to 0.51)	< 0.001
Anti-CCP antibody positivity	2.00 (1.63 to 2.45)	< 0.001	1.55 (1.18 to 2.05)	0.002
Vitamin D supplementation	0.54 (0.34 to 0.87)	0.011	0.47 (0.35 to 0.62)	< 0.001
CRP, mg/l	—	—	0.99 (0.99 to 1.00)	0.008
Tender joint count (0–28)	—	—	1.02 (1.01 to 1.04)	0.001

Anti-CCP: anti-cyclic citrullinated peptide antibody; CRP: C-reactive protein.

low 25-OH-D concentrations[1,2]. Our data are consistent with a recently published report showing high rates of vitamin D insufficiency (25-OH-D < 15 ng/ml) in African Americans with early RA[31]. The discrepancy in 25-OH-D concentrations in African Americans compared to white populations has been attributed to the inability of the skin to adequately produce vitamin D from ultraviolet B radiation exposure as a result of increased cutaneous melanin[32,33] and possible variation in dietary intake among African Americans. Two enrollment sites (Salt Lake City and Omaha) were at borderline northern latitude (40.47° N and 41.15° N, respectively), above which there is insufficient sun exposure for cutaneous vitamin D synthesis from the months of November through February[27]. Latitudes below 34° N (2 enrollment sites, Dallas and Jackson) allow for sufficient cutaneous vitamin D synthesis throughout the year[33]. However, latitude of the enrollment sites did not appear to affect our results, since rates of insufficiency did not vary substantially by study site (data not shown), and this further validates our findings.

Existing data indicate the immune effects of vitamin D are mediated through the vitamin D receptor (VDR), resulting in inhibition of proinflammatory T cells and dendritic cell differentiation. VDR agonists also lead to induction of T regulator and natural killer cells, resulting in suppression of autoimmunity[5,34]. Concentrations of 25-OH-D have been evaluated in RA patients in terms of its associations with disease risk and disease activity in only a few studies, with target populations of mainly female patients[10,11,12,13,14,35,36,37]. Data are equivocal regarding the role of vitamin D in the risk of onset of RA disease[11,12,13], with one prospective study showing an increased risk of RA

with low vitamin D intake[9] and another showing no association[8]. In a report of non-RA subjects, low 25-OH-D levels were found to be more frequent during the winter months and to be the result of decreased activity in patients leading to less sun exposure[38]. Results from that study suggest that levels of physical activity (not measured in our study) could serve as an important source of confounding. Low 25-OH-D levels (< 31.25 ng/ml) have been reported to be present in 16% of patients with RA, with lower levels associated with higher RA disease activity, similar to another study evaluating 108 RA patients[36,37]. An inverse association of 25-OH-D concentration with greater disease activity was supported in a cohort of 206 patients with early inflammatory polyarthritis (median duration 4 mo), with higher tender joint counts and worse Health Assessment Questionnaire scores observed in those with lower 25-OH-D concentrations[14]. Our study is the largest cohort (~ 1000 patients) to date that has examined the associations of vitamin D status with disease activity. Although we found associations of high hs-CRP levels and tender joint counts with vitamin D deficiency, there was no correlation of low 25-OH-D levels with composite scores of disease activity. Despite reports of generalized, persistent musculoskeletal pain with vitamin D insufficiency in non-RA populations[38,39], there was no correlation of low 25-OH-D status with pain scores in our study cohort.

To our knowledge, our results are the first to demonstrate an association of low 25-OH-D status with the anti-CCP antibody in patients with RA. However, there was no association of vitamin D status with other measures of RA disease severity including RF positivity, the presence of radiographic damage, or subcutaneous nodules. A study evaluating a variety of hormonal and metabolic variables in a heterogeneous group of patients with immune-mediated rheumatic diseases found no association with the anti-CCP antibody[40]. In individuals who were either anti-CCP antibody or RF-positive, but without clinical evidence of RA, evaluation of 25-OH-D levels found no difference between cases and negative autoantibody controls[41]. The latter study was limited by the very small number of unaffected subjects with anti-CCP antibody positivity. Prospective trials are needed to assess whether sustained low vitamin D levels in patients who are at increased risk for the development of autoimmune disease exert additional risk for development of RA, or simply serve as surrogates for patients with more severe disease that are less mobile and at risk for less sun exposure. Regardless, our data suggest that anti-CCP status may be an important consideration in a "case-finding" approach of targeting selected RA patients for 25-OH-D measurement.

There are limitations to this study. The results may not be applicable to the general population or other RA populations as our cohort consisted of US veterans, primarily elderly men. Our findings are, however, relevant, as it is important to recognize that the VHA currently represents the largest integrated health system in the US, with the number of beneficiaries with RA estimated to exceed 60,000. This was a cross-sectional study, therefore preventing causal inferences specific to the relationship of vitamin D status with measures of disease activity in RA. Although we adjusted for DMARD use, it is possible that treatments occurring prior to the study assessment could serve as a source of unmeasured confounding. We accounted for the use of vitamin D supplements through patient-reported over the counter use and dispensing of vitamin D supplementation as recorded in the PBM database, but we were not able to adjust for measures of adherence, dietary intake, or physical activity, all of which could influence rates of vitamin D insufficiency.

Recognizing our population was unique, including appropriate disease controls, such as patients with other inflammatory rheumatic and nonrheumatic diseases from similar settings would be informative. However, the strength of our study is that it is the largest cohort study of patients with RA to date that has evaluated the prevalence and correlations of vitamin D status; and is unique in its gender predominance of males, an often understudied subset.

25-OH-D insufficiency is common in US veterans with RA and is associated with disease severity, not clinical disease activity. With a prevalence of vitamin D insufficiency that is nearly universal, means for effective screening and appropriate supplementation, as well as the implications regarding costs, utilization, and strategies of implementation, need to be studied further.

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