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## Association of Vitamin D with Cardiometabolic Risk Factors in Rheumatoid Arthritis

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### Abstract

**Objectives**—Individuals with rheumatoid arthritis (RA) are at a greater risk for cardiovascular disease (CVD). Vitamin D deficiency is a potential risk factor for CVD and metabolic syndrome. Since patients with RA have a high prevalence of vitamin D deficiency, we investigated the association of vitamin D levels with cardiometabolic risk factors in a cohort of RA patients with no prior history of CVD.

**Methods**—Serum 25(OH)D levels were measured among RA patients enrolled in a cohort study of subclinical CVD. The cross-sectional associations of 25(OH)D level with traditional CVD risk factors, such as insulin resistance [estimated using the Homeostatic Model Assessment (HOMA)], adipokines, markers of systemic inflammation and endothelial activation were explored, adjusting for pertinent sociodemographic, lifestyle, and RA characteristics.

**Results**—Among 179 RA patients, 73 (41%) had a 25(OH)D level <30ng/mL. Only 23 patients (13%) had a 25(OH)D level ≥45ng/mL. After adjusting for demographics and BMI, 25(OH)D remained significantly associated with HDL and inversely associated with HOMA-IR, fibrinogen, E-selectin, and s-ICAM. Significant associations with HDL, E-selectin, and s-ICAM were maintained after adjusting for DAS28 and autoantibody status. These associations were similar between groups subdivided by gender, ethnicity, body mass index, DAS28 level and autoantibody status.

**Conclusions**—These data suggest that vitamin D deficiency is common in RA and may be independently associated with several cardiometabolic intermediates in this population.

Rheumatoid arthritis (RA) is a systemic inflammatory arthritis associated with increased morbidity and mortality, primarily related to greater atherosclerotic burden. Compared to non-RA controls, patients with RA are at a 1.5–3 fold increased risk of cardiovascular events (1, 2). The risk factors contributing to this increased propensity towards atherosclerosis in RA are poorly understood and have been a focus of expanding research. RA specific risk factors, such as chronic systemic inflammation (3), altered lipid function (4) and change in body composition (5) have been identified as few of the possible mechanisms driving the increased cardiovascular risk. Thus, identification of these and other risk factors is critical as their modification may result in improved long term outcomes in the RA population.

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Vitamin D deficiency has been associated with atherosclerosis and cardiometabolic risk factors, such as insulin resistance (6) hypertension (7) metabolic syndrome (8) and cardiovascular events (9, 10) in cross-sectional analyses of non-RA populations. In a meta-analysis of 28 studies, the highest levels of serum 25(OH)D were associated with a 43% reduction in cardiometabolic disorders, (ie CVD, DM and metabolic syndrome) [OR 0.57, 95% CI 0.48–0.68] (11). However, not all studies have confirmed these associations (12).

Vitamin D is a pleiotropic steroid molecule and exerts its physiological effects through the ubiquitous vitamin D receptor, a nuclear hormone receptor (13). Activated vitamin D is now implicated in regulating several genes with diverse biological functions (14, 15) which may explain its possible epidemiological associations with diverse chronic diseases, such as common cancers, cardiovascular disease (CVD) and autoimmune disorders (16, 17). Vitamin D also has known immunomodulatory effects (18) and its possible role in initiation and exacerbation of autoimmune diseases is an area of ongoing scientific study.

Low levels of vitamin D are noted to be common in RA, with several studies indicating greater than 50% prevalence of suboptimal vitamin D levels in this population (19, 20). Our data suggest that up to 60% of RA patients have suboptimal vitamin D levels in the mid-Atlantic region (21).

It is plausible that vitamin D deficiency in RA may pose an independent risk of cardiometabolic disease and thus may provide a modifiable target to potentially reduce cardiovascular disease burden in this population. However, any possible link between vitamin D deficiency and cardiometabolic risk factors in RA has not been evaluated. We thus investigated the relationship of vitamin D levels with cardiometabolic risk factors in a cohort of RA patients without established CVD and hypothesized that low vitamin D levels would be associated with greater cardiometabolic burden this population.

## PATIENTS AND METHODS

### Participants and Enrollment

Study subjects were participants in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE RA) Study, a cohort study investigating the prevalence, progression, and risk factors for subclinical CVD in RA patients described previously (22). Participants were 45 to 84 years of age at enrollment and met the American College of Rheumatology (formerly the American Rheumatism Association) 1987 classification criteria for RA (23). Exclusion criteria were known prior CVD defined as a prior history of self-reported physician-diagnosed myocardial infarction, heart failure, coronary artery revascularization, angioplasty, peripheral vascular disease or procedures (excluding varicose vein procedures), implanted pacemaker or defibrillator devices, and current atrial fibrillation. The study was approved by the Institutional Review Board of the Johns Hopkins Hospital, with all subjects providing written informed consent.

### Assessments

Clinical data and laboratory assessments derive from the second ESCAPE RA study visit, which occurred a median of 20 months after the baseline visit. Among the 197 participants enrolled at baseline, 186 completed the second study visit (a 94% retention rate).

**Sociodemographic, Lifestyle, and Body Composition Assessments**—Age, gender, race/ethnicity, educational attainment, and current and past smoking were assessed from patient-self report. Physical activity was assessed with the 7-Day Physical Activity Recall Questionnaire (24) with the weekly total of physical activity for intentional exercise

activities (moderate or brisk walking for exercise, and moderate or vigorous individual or team sports and conditioning activities) calculated for each participant. Diabetes was defined as a fasting serum glucose >126 mg/dL or use of anti-diabetic agents. Anthropometric measures (height, weight, body mass, index (BMI), and waist and hip circumferences) were assessed as previously described (22).

**RA Disease Characteristics**—Forty-four joints were examined for swelling, tenderness, deformity, and surgical replacement or fusion by a single trained assessor. RA disease duration was assessed by patient self-report from the date of diagnosis. RA disease activity was calculated using the Disease Activity Score for 28 joints with CRP (DAS28-CRP) (25). Current and past use of glucocorticoids, biologic and non-biologic disease modifying antirheumatic drugs (DMARDs) was queried by detailed examiner-administered questionnaires.

The 21-item Stanford Health Assessment Questionnaire (HAQ) (26) was used to assess disability related to common activities. Single view, anterior-posterior radiographs of the hands and feet were obtained and scored using the Sharp-van der Heijde (SvH) method (27) by a single, trained radiologist blinded to patient characteristics.

**Cardiovascular Risk Factor Assessments**—Diabetes was defined as a fasting serum glucose >126 mg/dL or use of anti-diabetic agents. Insulin resistance was estimated from fasting serum glucose and insulin using the Homeostatic Model Assessment 2 (28). Blood pressure was measured three times in the seated position using an automated device after a five minute period of rest in a quiet room. The average of the last two measurements was used in the analysis. Cuff size was determined based on arm circumference per standardized protocol.

**Laboratory Assessments**—Fasting serum and plasma samples were collected on the day of body composition analysis and stored at  $-70$  degrees C. 25(OH)D levels were measured using the standardized Diasorin radioimmunoassay. Vitamin D deficiency was defined as 25(OH)D level < 30 ng/ml, per expert consensus (29). C-reactive protein (CRP), fibrinogen, homocysteine, E-selectin, s-ICAM-1, adiponectin, resistin, leptin, and PAI-1 were measured at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT) as previously described (30). Fasting lipids were measured at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, MN). LDL-cholesterol was estimated in plasma specimens having a triglyceride value <400 mg/dL using the formula of Friedewald (31). Rheumatoid factor (RF) was assessed by ELISA, with seropositivity defined  $\geq 40$  units. Anti-CCP antibody was assessed by ELISA, with seropositivity defined  $\geq 60$  units.

## Statistical Analysis

The distributions of all variables were examined. Means and standard deviations were calculated for all normally distributed continuous variables and medians and interquartile ranges were calculated for continuous variables that were not normally distributed. For categorical variables, counts and percentages were calculated. The associations of patient characteristics were explored according to levels of 25(OH)D categorized as deficient (<30ng/mL), low sufficient (30–44.99 ng/mL), and high sufficient ( $\geq 45$ ng/mL) using ANOVA for normally distributed continuous variables, the Kruskal-Wallis test for non-normally distributed continuous variables, and the Chi-square or Fisher's exact test (as appropriate) for dichotomous variables. Ordinary linear regression was used to model the association of sociodemographic, lifestyle, body composition, and RA disease and treatment characteristics with 25(OH)D level, with  $\beta$  coefficients and their associated 95% confidence

intervals (CIs) and p-values calculated. Characteristics associated with 25(OH)D in multivariable modeling were retained as adjustment covariates in subsequent models including cardiometabolic risk factors. The Shapiro-Wilk test confirmed that assumptions of normality were met for all multivariable models in which non-transformed 25(OH)D was the dependent variable.

The associations of 25(OH)D with cardiometabolic risk factors were explored first by calculating Spearman correlation coefficients. Next, the changes in 25(OH)D level associated with each unit increase in cardiometabolic risk factors were calculated for each risk factor using ordinary linear regression, first in simple models with the cardiometabolic risk factor as the only covariate (with variables transformed to normality as required). Next, multivariable models were constructed adjusting for the confounding covariates identified from preliminary modeling (above). Non-linear associations of cardiometabolic risk factors with 25(OH)D level were explored by comparing adjusted mean risk factor levels across the extent of 25(OH)D categorized into quartiles, also using multivariable linear regression. Heterogeneity in the associations of cardiometabolic risk factors with 25(OH)D according to strata of demographic (gender, ethnicity), BMI (dichotomized at the median), seropositivity for RF or anti-CCP, and DAS28 (dichotomized at the median) were explored using ANCOVA.

All statistical calculations were performed using Intercooled Stata 10 (StataCorp, College Station, TX). In all tests, a two-tailed  $\alpha$  of 0.05 was defined as the level of statistical significance.

## RESULTS

Among the 186 ESCAPE RA participants who completed their second study visit, 179 had 25(OH)D levels measured. Of these, 73 (41%) were vitamin D deficient (25(OH)D < 30 ng/mL) and only 23 (13%) had a 25(OH)D level  $\geq$  45 ng/mL. The mean 25(OH)D level was  $34 \pm 10$  ng/mL. Participant characteristics according to 25(OH)D status are summarized in Table 1. In unadjusted comparisons, compared to RA patients with 25(OH)D levels  $\geq$  45 ng/mL, those with deficient levels (25(OH)D < 30 ng/mL) were significantly more likely to be non-Caucasian (91 vs. 79%, respectively;  $p=0.019$ ) and had a higher mean BMI (by an average of 1.6 units;  $p=0.059$ ). Age, sex, education, reported exercise, smoking did not differ by 25(OH)D status.

Among RA characteristics, those with deficient 25(OH)D levels were more likely to be RF or anti-CCP seropositive compared to those with 25(OH)D levels  $\geq$  45 ng/mL (82 vs. 64%, respectively;  $p=0.066$ ). Mean DAS28 was significantly higher among participants with deficient 25(OH)D compared to the group with a level  $\geq$  45 ng/mL (3.4 vs. 2.8 units, respectively;  $p=0.015$ ), with differences reflected in both higher median swollen and tender joint counts among those with deficient 25(OH)D. Other RA disease and treatment characteristics were not associated with 25(OH)D level. In a multivariable model also adjusting for season of assessment, lower 25(OH)D levels were significantly associated with non-Caucasian ethnicity, higher BMI, RF or anti-CCP seropositivity, and DAS28 (data not shown). These covariates were retained in subsequent multivariable models.

### Association of 25(OH)D with Cardiometabolic Risk Factors

The distributions of selected cardiometabolic risk factors are summarized in Table 2. Among these, increasing 25(OH)D demonstrated modest yet statistically significant biologic correlation with higher HDL-C, and inverse correlation with LDL-C, HOMA-IR, CRP, fibrinogen, E-selectin, and s-ICAM (Table 3). Trends to significance were observed in the

positive correlation of 25(OH)D with adiponectin and the inverse correlation of 25(OH)D with leptin.

After adjusting for gender, ethnicity, and season of assessment (Table 3, Adjusted Model 1), 25(OH)D remained significantly associated with HDL and adiponectin, and inversely associated with HOMA-IR, CRP, fibrinogen, E-selectin, and s-ICAM. The magnitude of the association of 25(OH)D with CRP and adiponectin was reduced, and statistical significance lost, after adjusting for BMI (Table 3, Adjusted Model 2). Subsequent adjustment for RF or anti-CCP seropositivity and DAS28 further reduced the magnitude of association of 25(OH)D with all of the cardiometabolic risk factors; however, statistically significant associations were maintained for HDL-C, E-selectin, and s-ICAM (Table 3, Adjusted Model 3).

The associations of 25(OH)D level with HDL and E-selectin were not linear across the extent of 25(OH)D. The adjusted mean HDL was 9 mg/dL lower for participants in the lowest quartile of 25(OH)D (6 – 25 ng/mL) compared to those in the upper three quartiles (49 vs. 58 mg/dL, respectively; a difference of 16% ( $p=0.004$ )) (Figure 1, Panel A). However, the adjusted mean HDL was not significantly different between those in the upper three quartiles. The adjusted mean E-selectin was 7 ng/mL higher for participants in the lowest quartile of 25(OH)D compared to those in the upper three quartiles (56 vs. 49 ng/mL, respectively; a difference of 20% ( $p=0.072$ )) (Figure 1, Panel B). However, the adjusted mean E-selectin was not significantly different between those in the upper three quartiles. In contrast, the adjusted mean s-ICAM decreased linearly with higher 25(OH)D levels by an average of 11 ng/mL per quartile increase in 25(OH)D ( $p=0.020$  for the linear trend across 25(OH)D; Figure 1, Panel C).

### **Differences in the Association of 25(OH)D with Cardiometabolic Risk Factors According to Strata of Patient Characteristics**

There was no evidence of significant heterogeneity in the association of 25(OH)D level with cardiometabolic risk factors between groups stratified by gender, ethnicity, BMI, or DAS28 level (data not shown).

## **DISCUSSION**

In this study, we observed a significant cross-sectional association between lower vitamin D levels and several cardiometabolic risk factors in a cohort of RA patients. Specifically, 25(OH)D had a significant inverse association with E-selectin and s-ICAM and a positive association with HDL even after adjusting for several potential confounders, including RA disease activity. These findings are novel and this is the first report implicating vitamin D deficiency as a possible cardiometabolic risk factor in RA. The association of HDL and E-selectin levels with quartiles of 25(OH)D was noted to be non-linear whereas the relationship between s-ICAM and 25(OH)D was linear.

We also observed a high prevalence (41%) of vitamin D deficiency in this cohort, consistent with previous publications (19, 20). Also consistent with other reports (32, 33), vitamin D deficiency was higher among non-Caucasian and obese individuals among our cohort of RA patients. Significant associations of 25(OH)D levels with insulin resistance, LDL and adiponectin were attenuated after adjusting for demographic confounders, BMI and RA disease activity. Thus, the association of 25(OH)D levels with these metabolic risk factors could be partially explained by BMI and RA disease activity. Similar confounding was observed in a cohort of 181 SLE patients, where lower levels of vitamin D were significantly associated with higher diastolic BP, LDL, cholesterol, fibrinogen, self reported

hypertension and diabetes. Most of these associations, however, became insignificant after adjustment for BMI (34).

Our findings in RA patients are consistent with previous reports of non-RA populations suggesting a relationship between low 25(OH)D concentration and prevalent cardiometabolic outcomes (35, 36). For example, analysis of NHANES III data showed that patients with the lowest 25(OH)D levels had a significantly higher prevalence of diabetes mellitus, hypertension and insulin resistance (7) compared to those with higher levels. Inverse association between vitamin D levels and cardiovascular events has also been reported in several cross-sectional (37–39) and prospective studies, including incident cardiovascular disease in the Framingham Offspring study (9, 40). However, other studies do not support this association and data from the few vitamin D supplementation studies and cardiovascular outcomes are inconclusive (41). Moreover, the long term safety of high dose vitamin D supplementation is an area of ongoing research.

In our study, we did not evaluate the association of 25(OH)D levels with cardiovascular events but explored its association with traditional risk factors that predispose to future CVD. Understanding these potential associations would be critical in our ability to modify these risks and possibly improve long term cardiovascular outcomes in RA.

There are several possible mechanisms governing the association between 25(OH)D and cardiometabolic risk factors. For one, pancreatic beta-cell function has been shown to be impaired at low levels of 25(OH)D (35). In addition, activated vitamin D regulates the renin-angiotensin system (42) and suppresses proliferation of vascular smooth muscles (43), potentially contributing to hypertension when vitamin D levels are suppressed. E-selectin and s-ICAM are vascular adhesion molecules that have been implicated in pathogenesis of atherosclerosis (44, 45). *In vitro* data suggest that activated vitamin D analogs modulate the expression of vascular adhesion molecules (46, 47), another mechanism through which vitamin D deficiency may potentiate atherogenesis. Our study is the first to report an inverse association between low levels of vitamin D and E-selectin/s-ICAM in RA.

Adiponectin is one of the several adipocytokines secreted by adipose tissue. Low adiponectin levels may be an independent risk factor for insulin resistance (48, 49) and atherosclerosis (50, 51). An association between vitamin D deficiency and low adiponectin levels was observed in individuals with abnormal glucose tolerance, independent of adiposity (52), suggesting that adiponectin may be a link between vitamin D and insulin resistance. We report a similar relation between 25(OH)D and adiponectin levels in RA; that is low levels of 25(OH)D correlated with low adiponectin levels. This association became insignificant in our cohort after controlling for BMI. However, these preliminary data point towards a possible relationship between adipokines and vitamin D in RA, which should be further explored.

Vitamin D deficiency in our cohort was associated with autoantibody seropositivity and increased RA disease activity as measured with DAS28-CRP, and its components of tender and swollen joint counts. This is consistent with previous publication(19) in which anti-CCP seropositivity was associated with an approximately 2-fold increased risk of vitamin D deficiency in a cohort of US veterans with RA. Similarly, inverse associations of 25(OH)D levels with DAS28-CRP and tender joint counts have also been shown in previous studies (53, 54).

Among study limitations, our observational data are hypothesis generating and these findings should be considered preliminary. Being cross-sectional, the temporality of association and causality cannot be established, as we are not able to determine whether vitamin D deficiency is a risk factor for metabolic syndrome in RA or whether the reverse

may be true. Vitamin D deficiency is known to be associated with obesity, sedentary life style and may be a surrogate marker for overall poor health. We attempted to account for these established confounders by adjusting accordingly in our models; however, there remains the possibility for residual confounding due to measurement error or unaccounted for confounders.

In conclusion, we observed significant associations between low 25(OH)D levels and higher levels of several cardiometabolic risk factors, as well as increased disease activity, in a cohort of RA patients. These preliminary findings may have broad clinical implications in management of RA. However, further studies are required to validate these observations and to determine if vitamin D deficiency, via its association with cardiometabolic risk factors translates to clinical cardiovascular end points in patients with RA.

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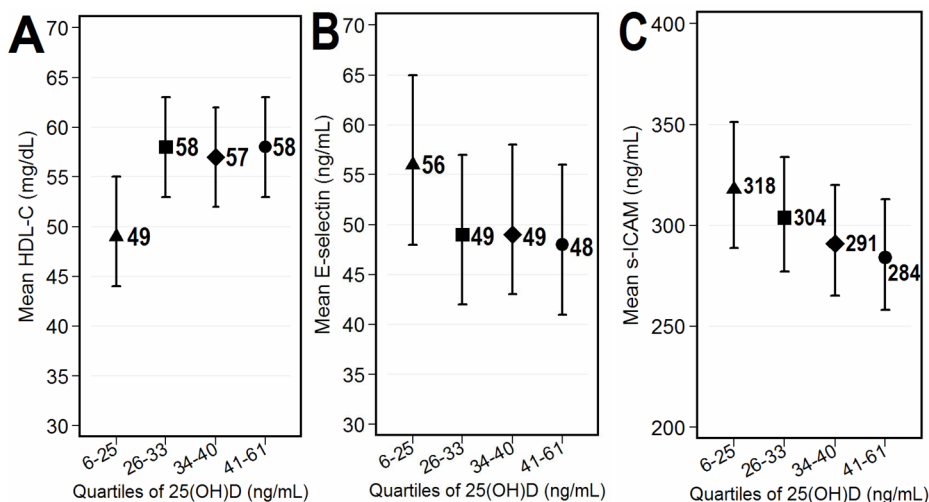


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### Significance and Innovation

- Our study is the first to explore the relationship between vitamin D levels and cardiometabolic risk factors in individuals with rheumatoid arthritis (RA).
- Our data suggests that vitamin D deficiency in individuals with RA may be independently associated with several cardiometabolic risk factors.
- These are hypothesis generating data, and suggest the need for further evaluation of possible role of vitamin D as a novel therapeutic target to reduce cardiovascular risk in RA.



**Figure 1.** Graphs depict adjusted means and 95% confidence intervals for cardiometabolic according to quartiles of 25(OH)D. Analyses were adjusted for gender, ethnicity, body mass index, season, rheumatoid factor or anti-CCP seropositivity, and DAS28. In panel A, the p-value for the comparison of the adjusted mean HDL-C between the lowest quartile of 25(OH)D and the combined upper three quartiles was 0.004. In panel B, the p-value for the comparison of the adjusted mean E-selectin between the lowest quartile of 25(OH)D and the combined upper three quartiles was 0.072. In panel C, the p-value for the linear trend in adjusted mean s-ICAM over the extent of 25(OH)D was 0.020.

Table 1

Participant Characteristics According to 25-OH Vitamin D Status

	Total (n = 179)	25(OH)D < 30 (n = 73)	25(OH)D 30 – 44.99 (n = 83)	25(OH)D 45 (n = 23)	p
Age, years	61 ± 8	61 ± 8	62 ± 9	61 ± 8	0.63
Male, n (%)	69 (39)	23 (32)	35 (42)	11 (48)	0.24
Caucasian, n (%)	157 (88)	58 (79)	78 (94)	21 (91)	0.019
Any college, n (%)	132 (74)	56 (77)	61 (74)	15 (65)	0.55
Body mass index, kg/m <sup>2</sup>	28.6 ± 5.3	29.1 ± 5.5	28.6 ± 5.2	27.5 ± 5.0	0.059
Waist circumference, cm	95 (85 – 106)	93 (86 – 108)	95 (84 – 106)	95 (82 – 103)	0.78
Habitual exercise, min/day	34 (4 – 75)	33 (5 – 69)	30 (0 – 64)	47 (9 – 120)	0.24
Diabetes, n (%)	11 (6.2)	4 (6)	5 (6)	2 (9)	0.82
Ever smoking, n (%)	100 (56)	42 (58)	47 (57)	11 (48)	0.67
Current smoking, n (%)	21 (12)	13 (18)	5 (6)	3 (13)	0.75
Hormone replacement; (women), n (%)	16 (15)	6 (12)	7 (15)	3 (25)	0.54
RA duration, years	10.5 (6 – 18.5)	10 (7 – 18)	11 (6 – 20)	11 (5 – 19)	0.94
RF or anti-CCP seropositivity, n (%)	137 (77)	60 (82)	63 (76)	14 (64)	0.066
Any shared epitope alleles, n (%)	124 (70)	50 (69)	59 (72)	15 (65)	0.70
DAS28-CRP	3.2 ± 1.1	3.4 ± 1.1	3.1 ± 1.0	2.8 ± 0.9	0.015
Swollen joints (0–42)	3 (2 – 6)	4 (2 – 9)	3 (2 – 6)	3 (0 – 6)	0.026
Tender joints (0–44)	5 (2 – 13)	6 (2 – 14)	5 (2 – 12)	2 (0 – 14)	0.062
HAQ (0 – 3)	0.75 (0.13–1.50)	0.75 (0.13–1.63)	0.75 (0.13–1.25)	0.25 (0–1.50)	0.27
Baseline total SvH score	43 (15 – 116)	55 (21 – 123)	33 (13 – 85)	38 (12 – 121)	0.31
Duration of morning stiffness, minutes	15 (4 – 30)	15 (3 – 45)	15 (3 – 30)	15 (5 – 45)	0.66
Pain (100mm VAS)	21 (6 – 46)	20 (9 – 43)	22 (5 – 49)	20 (4 – 50)	0.68
Current prednisone, n (%)	67 (39)	27 (39)	30 (37)	10 (43)	0.86
Cumulative prednisone, grams	4.6 (0.2 – 11.3)	4.0 (0.9 – 8.3)	5.4 (0.1 – 10.6)	4.3 (0 – 11.7)	0.76
Current non-biologic DMARDs, n (%)	151 (87)	61 (87)	70 (86)	20 (87)	0.99
Current biologic DMARDs, n (%)	84 (48)	33 (47)	39 (48)	12 (52)	0.92

Values are depicted as mean ± SD or median (interquartile range) unless otherwise noted

RA=rheumatoid arthritis; RF=rheumatoid factor; CCP=cyclic citrullinated peptide; DAS=disease activity score; CRP=C-reactive protein; HAQ=health assessment questionnaire; SvH=Sharp van der Heijde Score; VAS=visual analogue scale; DMARD=disease modifying anti-rheumatic drug

Table 2

## Cardiometabolic Risk Factors Among 179 RA Patients

	Total (n = 179)
Systolic blood pressure, mm Hg	131 (117 – 145)
Diastolic blood pressure, mm Hg	78 (71 – 84)
LDL-C, mg/dL	107 (85 – 125)
HDL-C, mg/dL	53 (40 – 70)
Triglycerides, mg/dL	100 (69 – 142)
Fasting glucose, mg/dL	91 (85 – 98)
HOMA-IR	0.80 (0.50 – 1.40)
CRP, mg/L	2.8 (1.0 – 7.20)
Fibrinogen	364 (296 – 439)
Homocysteine	9.7 (8.0 – 12.1)
E-selectin	49 (38 – 68)
s-ICAM	296 (247 – 361)
Adiponectin, mg/L	35 (21 – 46)
Resistin, ng/mL	14 (11 – 18)
Leptin, ng/mL	15 (7 – 30)
PAI-1, ng/mL	16 (11 – 23)

Values depicted are median (interquartile range)

RA=rheumatoid arthritis; LDL=low density lipoprotein; HDL=high density lipoprotein; HOMA=homeostatic model assessment; CRP=C-reactive protein; PAI=plasminogen activator inhibitor

**Table 3**  
Crude and Adjusted Associations of Cardiometabolic Risk Factors with Vitamin D Levels (ng/mL)

	Spearman Correlation		Linear Regression Models: Change in 25(OH)D per unit change in cardiometabolic risk factor							
	With 25(OH)D	r	Unadjusted Model	Adjusted Model 1	Adjusted Model 2	Adjusted Model 3	β	p		
Systolic blood pressure	-0.024	ns								
Diastolic blood pressure	0.006	ns								
LDL-C	-0.167	0.028	-0.050	0.049	-0.040	0.13	-0.038	0.14	-0.046	0.066
HDL-C	0.157	0.037	0.094	0.021	0.136	0.002	0.110	0.018	0.097	0.035
log triglycerides	-0.001	ns								
Fasting glucose	-0.118	ns								
log HOMA-IR	-0.202	0.007	-3.10	0.006	-3.25	0.003	-2.62	0.029	-1.75	0.17
log CRP	-0.177	0.018	-1.34	0.023	-1.29	0.029	-1.10	0.061	-0.43	0.51
log fibrinogen	-0.231	0.002	-8.63	0.004	-8.47	0.006	-7.32	0.018	-4.95	0.12
log homocysteine	0.028	ns								
log E-selectin	-0.162	0.030	-4.73	0.001	-4.48	0.002	-4.40	0.003	-3.52	0.023
log s-ICAM	-0.174	0.020	-6.69	0.007	-7.52	0.002	-7.24	0.003	-5.83	0.020
log adiponectin	0.143	0.061	2.63	0.042	2.85	0.041	2.41	0.089	2.20	0.11
log resistin	0.020	ns								
log leptin	-0.127	0.092	-1.03	0.18	-0.66	0.44	1.49	0.21	1.31	0.26
log PAI-1	-0.050	ns								

Model 1: adjusted for gender, ethnicity, and season

Model 2: adjusted for Model 1 covariates + body mass index

Model 3: adjusted for Model 2 covariates + RF/anti-CCP seropositivity status and DAS28