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Rheumatol Int. Author manuscript; available in PMC 2015 July 22.

Published in final edited form as:

Rheumatol Int. 2012 December ; 32(12): 3923–3929. doi:10.1007/s00296-011-2287-y.

25-hydroxyvitamin D levels and Juvenile Idiopathic Arthritis: is there an Association with Disease Activity?

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Abstract

Objectives—To examine the association between serum levels of 25-hydroxyvitamin D [25(OH)D] and disease activity in juvenile idiopathic arthritis (JIA), to determine the prevalence of vitamin D (VD) deficiency [25(OH)D≤19 ng/ml] and insufficiency [25(OH)D 20-29 ng/ml], and to determine factors associated with lower serum levels of 25(OH)D in this population.

Methods—In this cross-sectional study, disease activity was measured using JADAS-27, as well as its individual components (physician global assessment of disease activity, parent global assessment of child's well-being, count of joints with active disease, and erythrocyte sedimentation rate). Linear regression models were developed to analyze the association between serum 25(OH)D levels and JADAS-27, and to determine variables associated with serum 25(OH)D levels.

Results—154 patients (61% females, 88% whites) were included. Mean age was 10.6. VD deficiency was detected in 13% and insufficiency in 42%. In univariate and multivariate analyses, 25(OH)D levels were not associated with JADAS-27, neither with its individual components. However, in a subset analysis including all new onset JIA patients (n=27) there was a non-significant negative correlation between serum 25(OH)D levels and JADAS-27 (r=−0.29, p=0.14).

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The authors declare that they have no conflict of interest.

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In the univariate and multivariate analyses, age, ethnicity, BMI, and season were significantly associated with serum 25(OH)D levels, but not total VD intake.

Conclusions—More than 1/2 of JIA patients had serum 25(OH)D levels below 29 ng/ml, however there was no association between serum 25(OH)D levels and disease activity. Future larger, long-term studies with new-onset JIA patients are needed to further explore the association between serum 25(OH)D levels and disease activity.

Keywords

25-hydroxyvitamin D; Arthritis, Juvenile Rheumatoid; Inflammation

Introduction

Vitamin D plays an important role in the immune system and has multiple immunosuppressant properties [1-9]. Serum vitamin D levels have been negatively associated with disease activity in autoimmune disorders in adults across multiple observational studies [10-20]. For example, serum 25-hydroxyvitamin D [25(OH)D] levels have been found to correlate inversely with disease activity in adults with rheumatoid arthritis (RA) and in those with newly diagnosed inflammatory polyarthritis [21,22]. Similarly, serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] concentration has been found to be negatively correlated with disease activity in RA and ankylosing spondylitis [23,24].

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood and is an important cause of short- and long-term disability in children [25]. In a previous study we showed that children with autoimmune disorders, including JIA, were more likely to be vitamin D deficient than controls [26]. Similarly, others have showed decreased serum levels of 25(OH)D in children with JIA, compared to healthy controls [27]. However, the association between disease activity and serum levels of 25(OH)D demonstrated in adults with RA has not to our knowledge been reported in children with JIA. If this association exists in JIA, it may represent a promising therapeutic target.

The primary aim of this study was to examine the association between serum levels of 25(OH)D and disease activity in children and adolescents with JIA. The secondary aims were to determine the prevalence of vitamin D deficiency and insufficiency according to the conventionally used (but non-validated) cutoffs of serum 25(OH)D (≤19 ng/ml and 20-29 ng/ml) in children and adolescents with JIA, and to determine factors associated with lower serum levels of 25(OH)D in this population.

Methods

This was a cross-sectional study, conducted between October 2009 and September 2010, at the Pediatric Rheumatology clinic of the Floating Hospital for Children at Tufts Medical Center. Children and adolescents with JIA (subtypes: oligoarthritis, rheumatoid factor-positive polyarthritis, rheumatoid factor-negative polyarthritis, systemic-onset arthritis, enthesitis-related arthritis, and psoriatic arthritis), between the ages of 2 and 19 years, who

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had blood drawn for routine clinical monitoring and agreed to participate in the study were enrolled.

Subjects who had any conditions, or were using any medications, that would affect vitamin D metabolism were excluded. These conditions included: use of prednisone (any dose, on the previous 3 months), concurrent medical problems (diabetes type 1, inflammatory bowel disease, celiac disease, immunodeficiency), and pregnancy. Subjects with history of a recent infection (within 2 weeks) were also excluded, since this could increase the inflammatory markers used to measure JIA disease activity. This project was approved by the Institutional Review Board at Tufts Medical Center. Children 7 years or older signed assent forms and parents of minors signed consent forms. Participants who were 18 years or older signed consent forms themselves. From all subjects who were invited to participate in the study, only one declined.

Disease activity measurement was compiled using a previously validated score, JADAS-27 (Juvenile Arthritis Disease Activity Score 27) [28]. This score includes four measures: physician global assessment of disease activity using a visual analog scale (VAS), parent global assessment of child's well-being determined by a VAS, count of joints with active disease, and erythrocyte sedimentation rate (ESR). The physician assessment of disease activity is based on a 10 cm VAS, where 0 corresponds to no activity and 10 corresponds to maximum activity. The parent's assessment of child's well-being is also based on a 10 cm VAS, where 0 corresponds to very well and 10 to very poor. The count of active joints in JADAS-27 evaluates 27 joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles. Each active joint scores 1 point, and the total ranges from 0 to 27. ESR is normalized to a score ranging from 0 to 10, by the formula (ESR-20)/10. JADAS-27 is then calculated as the simple linear sum of the scores of its 4 components, which yields a total score of 0 to 57, with higher scores representing worse disease activity.

Serum 25(OH)D was measured by LC/MS/MS (Waters Acquity UPLC with TQD triple quadrupole mass spectrometer). This method separates and quantifies circulating $25(OH)D_2$ and $25(OH)D_3$. The lab participates in the College of American Pathologists proficiency testing and the Vitamin D External Quality Assessment Scheme (deqas.org), an international consortium of laboratories set up to ensure the analytical reliability of 25(OH)D. The lab also validated the assay using the Standard Reference Material (SRM 972), which was developed by the National Institute of Standards and Technology (NIST). Inter-assay CVs (coefficient of variation) are 6.5-11% for $25(OH)D_3$ over the range of 5-80 ng/mL and 9-13% for $25(OH)D_2$ over the range of 2.5-60 ng/mL.

A structured interview was conducted with parents. Participants who were 18 years or older completed this interview themselves. The structured interview was designed to collect important demographic and health information, including, child's age, gender, ethnicity, current medications, use of supplements containing vitamin D, use of oral contraceptives, history of recent travel or tanning, and diet history (food frequency questionnaire). JIA subtype, time interval since disease onset, date and season of evaluation, and body mass index (BMI) were determined by the investigators. Season in which the study visit was

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conducted was registered, since serum 25(OH)D levels vary considerably by season [29,2,30,9,31]. BMI was calculated dividing the weight (in kg) by the square of the height (in m). Children were classified as underweight if their BMI was under the 5th percentile, obese if their BMI was greater than or equal to the 95th percentile, and adequate if BMI was between the 5th and 94th percentiles [32]. Medications used for JIA treatment were documented (non-steroidal anti-inflammatory drugs, methotrexate, and biologic drugs including etanercept, adalimumab, infliximab, canakinumab, anakinra, and abatacept), as well as the duration of use of each medication. We only considered the use of methotrexate or a biologic drug if the duration of use was at least 2 months. The use of oral contraceptives was registered, as estrogens may influence serum 25(OH)D levels [33]. We also documented trips to areas of increased sun exposure, in relation to Boston, as well as tanning, since these 2 factors could influence serum 25(OH)D levels [34-36]. Vitamin D ingested from diet was calculated based on a food frequency questionnaire [26]. We estimated the total daily vitamin D intake, in IU, by adding the amount ingested from diet to any amount ingested from supplements.

Statistical analyses

Approximately 180 patients with JIA are seen at the Pediatric Rheumatology clinic in the Floating Hospital for Children each year. *A priori* sample size calculations showed that recruitment of 150 subjects would yield 80% power to detect a correlation between serum 25(OH)D levels and JADAS-27 of 0.23. Sample size calculation was constrained by feasibility, rather than a clinically meaningful correlation of 0.23.

Scatter plots of serum 25(OH)D levels and JADAS-27 results were constructed to examine linearity and to check for potential outliers. A linear regression model was developed to analyze the association between serum 25(OH)D levels and the outcome JADAS-27. The model was adjusted for potential confounders, identified *a priori*, including age, gender, JIA subtype, ethnicity (non-Hispanic whites versus others), medications (none, non-steroidal anti-inflammatory drugs, or immunosuppressants - methotrexate and/or biologics), season (summer versus others), and time since disease onset. We checked for interactions between serum 25(OH)D and medications, since we thought there could be a differential effect of serum 25(OH)D on disease activity at different levels of this variable. The variables ethnicity and season were collapsed into binary variables for the model to avoid overfitting.

The prevalence of vitamin D deficiency and insufficiency as defined by conventionally used cutoffs for serum 25(OH)D (≤19 ng/ml and 20-29 ng/ml) was determined. Despite being widely used in the literature, the cutoffs mentioned above have not been validated in children and therefore were not employed in our primary analyses [37,38].

Two approaches were used to determine factors associated with low serum 25(OH)D levels. We used a logistic regression model to identify variables associated with low vitamin D levels, defined as the lowest quartile of our sample [serum 25(OH)D <23 ng/ml], vs. higher levels of serum 25(OH)D (≥23 ng/ml). The variables of interest were: age (up to 10 years old vs. older than 10), ethnicity (non-Hispanic whites vs. other ethnicities), BMI (obese vs. non-obese), and season (summer vs. non-summer).

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A linear regression model was also developed to analyze the variables associated with serum 25(OH)D levels, including age, ethnicity (non-Hispanic whites vs. other ethnicities), BMI (obese vs. non-obese), season (summer vs. non-summer), and total daily vitamin D intake.

JMP version 8 (SAS Institute Inc., Cary, NC) was used for data analyses. $P<0.05$ was considered significant. We checked model diagnostics and goodness of fit for all 3 models.

Results

A total of 154 patients were enrolled and included in the analysis. Patient characteristics are shown in Table 1. The average age of participants was 10.6 years, 61% were female, and 88% were non-Hispanic white. The number of patients enrolled during each season was not significantly different (Table 2). Only a small number of patients were noted to have documented trips to areas of increased sun exposure or tanning (N=7) or to have used contraceptives (N=5). Among the 57 patients (37%) taking supplements containing vitamin D, the dose ranged from 400 to 2,400 IU of vitamin D_3. Total daily vitamin D intake ranged from 0.03 to 2,764 IU (Table 2).

The mean serum 25(OH)D level was 29.2 ng/ml. The lowest quartile of serum 25(OH)D consisted in levels <23.0 ng/ml; the second quartile included levels from 23.0 to <28.5 ng/ml; the third quartile was between 28.5 and 34.0 ng/ml and the highest quartile consisted of serum 25(OH)D above 34.0 ng/ml. The values of serum $25(OH)D_3$ and $25(OH)D_2$ are shown in Table 3. Serum 25(OH)D levels of 19 ng/ml or less were detected in 13% of patients and serum 25(OH)D levels from 20 to 29 ng/ml in 42% (Table 3).

The score of JIA disease activity, JADAS-27, had a median value of 5.2 (range 0 to 30.7). Results of the four components of JADAS-27 are detailed in Table 4.

In the univariate linear regression analysis serum 25(OH)D levels were not associated with JADAS-27 (beta coefficient=0.002; 95%CI= −0.1, 0.1; p=0.97), nor with any of the four separate components of JADAS-27 (p-value range 0.32-0.89).

A similar lack of association was found in multivariate linear regression analysis adjusting for age, gender, JIA subtype, ethnicity, JIA medications, season, and time since disease onset (p=0.67) (Table 5). However, this multivariate analysis revealed nominally significant associations between JADAS-27 and JIA subtype (p=0.003), and ethnicity (p=0.006). Patients with rheumatoid factor-positive polyarticular JIA had estimated JADAS-27 scores that were 4.9 points higher on average than patients with oligoarticular JIA. Non-Hispanic white patients had JADAS-27 scores that were 1.9 points lower, on average, than patients of all other ethnicities (Table 5).

In a subset analysis, we examined the correlation of serum 25(OH)D levels with JADAS-27 separately for all new onset (time since disease onset ≤ 3 months) JIA patients (N=27) as opposed to patients with long-term disease. This subset analysis was not planned *a priori*; we performed to explore whether measured and unmeasured confounders associated with long-term disease (e.g., medications, vitamin D supplementation, lifestyle) could be responsible for a falsely negative result. In this subset analysis, there was a non-significant

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negative correlation between serum 25(OH)D levels and JADAS-27 in new-onset patients (r=−0.29, p=0.14), while there was no correlation in patients with long-term JIA (r=0.06, p=0.52).

Regarding variables possibly associated with the lowest quartile of serum 25(OH)D levels, in the multivariate logistic regression analysis, ethnicities other than non-Hispanic white (OR=3.1; 95%CI=1.1, 8.7; p=0.04), and age older than 10 (OR=2.5; 95%CI=1.1, 5.5; p=0.03) were associated with higher odds of this endpoint.

In the multivariate linear regression analysis using serum 25(OH)D levels as the outcome, for each increase in age by 1 year, serum 25(OH)D decreased an estimated 0.3 ng/ml (p=0.04); non-Hispanic white patients had estimated serum 25(OH)D levels that were on average 2.6 ng/ml higher than other ethnicities (p=0.01); non-obese patients had estimated serum 25(OH)D levels that were 2.5 ng/ml higher, on average, than obese patients (p=0.006); and estimated serum 25(OH)D levels were on average 2.3 ng/ml higher in summer than in other times of year (p=0.01) (Table 6). Self-reported total vitamin D intake was not associated with serum 25(OH)D levels (p=0.86).

Discussion

There was no association between serum 25(OH)D levels and JIA disease activity, measured by JADAS-27, in either univariate or multivariate analyses, nor between serum 25(OH)D levels and individual JADAS-27 components.

Although we did not find an association between serum 25(OH)D levels and JADAS-27, there was a significant association between JIA subtypes with this disease activity score. This suggests that the overall null result of our primary analysis was unlikely to be due to substantial measurement error of disease activity or lack of meaningful variation in this outcome, since we did find the association that has been established before and was expected [25].

There are several reasons why we may have failed to detect an association between serum 25(OH)D levels and disease activity in patients with JIA. First, JIA is a different disease than RA [25], and the association between serum 25(OH)D levels and disease activity described in adult patients with inflammatory arthritis may not exist in childhood arthritis.

A second possibility is that we analyzed data from patients with established ongoing disease. These patients could have several measured and unmeasured confounders, which could induce the apparent lack of an existing association between serum 25(OH)D levels and disease activity. Many of these patients were taking methotrexate or a biologic drug, for example, which modifies the disease course. Considering this possibility, we conducted a subset analysis of new patients, in which we found an intriguing though statistically non-significant negative association between serum levels of 25(OH)D and JADAS-27. The lack of statistical significance of this finding could have been due to inadequate power, as there was a very small sample of new-onset JIA. Hence, future studies of the association between serum 25(OH)D levels and disease activity, enrolling only newly diagnosed JIA patients, may be useful.

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A third aspect to be considered is that chronic exposures, such as serum 25(OH)D levels in our study, may have different effects on short- or long-term outcomes [39]. The lack of an association between serum 25(OH)D levels and JIA disease activity measured at the same point in time does not preclude an association with disease activity in the long-term.

Another aspect to be considered is that the apparent effect of risk factors on exacerbations might be attenuated when there is congruence between the risk factors that cause the disease to develop in the first place and risk factors that cause an acute exacerbation [39]. It is not known if serum 25(OH)D levels are a risk factor for the development of JIA, but if so, the effects of serum 25(OH)D levels on JIA exacerbations could have been attenuated. We did not analyze patients enrolled in our study separately by disease flare or remission.

A fifth possibility for the lack of an association between serum 25(OH)D levels and JIA activity in our study is that there was confounding by vitamin D supplementation that was not captured in our model. While we collected information on current vitamin D supplementation, we did not capture information on duration of vitamin D supplementation. It is known that at least 3 months of vitamin D supplementation are necessary to reach a steady state and physiologic effects of vitamin D deficiency or insufficiency may persist for even longer [40]. These effects could obscure any relationship between cross-sectionally measured serum 25(OH)D levels and JIA disease activity.

Another possibility is that the association between serum 25(OH)D levels and disease activity in JIA might be weaker than our study would be able to detect, due to inadequate statistical power.

An interesting aspect of this study is that disease activity was worse in African American, Hispanic, and Asian patients. Although the association of ethnicity and JIA disease activity has not been published before, others have reported a higher incidence of rheumatoid factor-positive polyarticular JIA in non-white populations [41,42]. Several factors could be responsible for the worse disease activity in these minorities in our sample, including different socioeconomic status, cultural aspects, genetics, or even adherence to treatment. Future studies are needed to further explore JIA disease activity in different ethnicities.

The variables associated with serum 25(OH)D levels in this sample of children with JIA were the same as those described for healthy children and adults in other studies, including age, ethnicity, BMI, and season [29,34,43,35,36,31,9,44,30]. Unexpectedly, total vitamin D intake was not associated with serum 25(OH)D levels. The lack of association may have been due to recently initiated treatment of vitamin D deficient patients with high doses of vitamin D supplements who did not achieve steady state of serum 25(OH)D levels yet.

This study had some limitations, including the cross-sectional design, which impacted the probability of detecting an effect if serum 25(OH)D levels influenced disease activity over time. Also JADAS-27 as a measurement of disease activity has yet to be validated for enthesitis-related arthritis and psoriatic arthritis. However, we conducted separate analyses with the individual components of JADAS-27, which are used in clinical practice to determine disease activity. There is the possibility of selection bias, as only patients who were having blood drawn for clinical reasons were invited to be enrolled in the study.

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Nevertheless, the study enrolled patients during a period of one year, and virtually every patient with JIA would have blood drawn at least once a year.

The major strength of this study is that it was, to the best of our knowledge, the first study to examine the association between serum 25(OH)D levels and disease activity in children and adolescents with JIA. Another strength was the study duration of one year, which was important to register the seasonal variation in serum 25(OH)D levels, and also to maximize the number of patients enrolled. This study adds evidence to the growing knowledge regarding vitamin D and autoimmunity.

In conclusion, more than one half of JIA patients had serum 25(OH)D levels below 29 ng/ml, however there was no association between serum 25(OH)D levels and disease activity in this sample of children and adolescents with JIA. Age, ethnicity, BMI, and season were associated with serum 25(OH)D levels in patients with JIA. Future larger, long-term studies evaluating patients with new-onset JIA are needed to further explore and elucidate the association between serum 25(OH)D levels and disease activity.

Acknowledgement

We would like to thank Dr. Caitlin Sgarlat and Dr. Trevor Davis for the assistance with data collection.

The project described was supported by Award Number UL1 RR025752 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

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Table 1

Demographic characteristics of enrolled patients

Age (mean ± SD)	10.6 ± 4.5
Females % (N)	61% (94)
Ethnicity % (N)	
Non-Hispanic white	88% (135)
African American	2.5% (4)
Hispanic	7% (11)
Asian	2.5% (4)
JIA subtype % (N)	
Oligoarthritis	46% (71)
Rheumatoid factor-negative polyarthritis	21.5% (33)
Rheumatoid factor-positive polyarthritis	2.5% (4)
Systemic-onset arthritis	2.5% (4)
Enthesitis-related arthritis	19% (29)
Psoriatic arthritis	8.5% (13)
Time since JIA onset in months (median, IQR[a])	28, 6 – 66
Medications% (N) / **Time on medications** in months (median, IQR[a])	
Non-steroidal anti-inflammatory drugs - 50% (77)	8, 2 – 22
Methotrexate - 18% (28)	15, 7 – 47
Biologics - 16% (25)	19, 6 – 33
Intra-articular steroids - 4% (6)	N/A
None - 32.5% (50)	N/A

[a] IQR – interquartile range

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Table 2

Variables that could influence serum 25(OH)D levels

Season % (N)	
Fall	32% (49)
Winter	25% (39)
Spring	23.5% (36)
Summer	19.5% (30)
BMI[a] category % (N)	
Adequate	79% (122)
Obese	18% (28)
Underweight	3% (4)
BMI[a] absolute value (median, IQR[b])	18.6, 16.2 – 21.9
BMI[a] percentile (median, IQR[b])	67, 41 – 88
Vitamin D ingestion	
Dose of vitamin D_3 on supplements in IU (median, IQR[b])	400, 400 - 1,000
Vitamin D ingested from diet in IU (median, IQR[b])	239, 136 – 368
Total daily vitamin D intake in IU (median, IQR[b])	368, 172 - 687

[a] BMI – Body mass index,

[b] IQR – interquartile range

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Table 3

Serum 25(OH)D levels

Total serum 25(OH)D in ng/ml (mean ± SD, range)	29.2 ± 9.2, 6 – 58
Serum 25(OH)D_3 in ng/ml (mean ± SD, range)	27.9 ± 9.3, 6 – 58
Serum 25(OH)D_2 in ng/ml (mean ± SD, range)	1.3 ± 3.1, 0 – 29
Serum 25(OH)D ≤19 ng/ml % (N)	13% (20)
Serum 25(OH)D 20-29 ng/ml % (N)	42% (64)

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Table 4

JADAS-27 and its individual components

	Median	Interquartile range	Range
Parent VAS	1.4	0.6 – 2.8	0 – 8.9
Physician VAS	1.2	0.2 – 2.5	0 – 8
ESR normalized	0	0 - 0	0 - 8.2
Joint count	2	0 - 4	0 – 18
JADAS-27	5.2	2 – 10.1	0 – 30.7

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Table 5

Multivariate linear regression analysis of the effect of serum 25(OH)D levels on JADAS-27

Term	Estimate	Standard Error	95% Confidence interval	p-value
Serum 25(OH)D (ng/ml)	0.02	0.05	−0.08, 0.12	0.67
Age (years)	−0.01	0.13	−0.26, 0.24	0.92
Gender (male)	0.007	0.48	−0.93, 0.95	0.98
JIA subtype				0.003
Oligoarthritis	Reference group			
Psoriatic arthritis	−1.78	1.49	−4.70, 1.14	0.23
RF[a]-negative polyarthritis	1.75	1.10	−0.41, 3.91	0.11
RF[a]-positive polyarthritis	4.94	2.47	0.10, 9.78	0.05
Systemic-onset arthritis	−0.16	2.39	−4.84, 4.52	0.94
Enthesitis-related arthritis	−1.68	1.22	−4.07, 0.71	0.17
Ethnicity (non-Hispanic white)	−1.94	0.70	−3.31, −0.57	0.006
Medications				0.13
Methotrexate and/or biologics	Reference group			
NSAIDs[b] only	0.77	0.66	−0.52, 2.06	
None	−1.36	0.68	−2.69, −0.03	
Season (non-Summer)	0.09	0.61	−1.11, 1.29	0.87
Time since disease onset (months)	−0.0005	0.01	−0.02, 0.02	0.96

[a] RF – Rheumatoid factor,

[b] NSAIDs – non-steroidal anti-inflammatory drugs

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Table 6

Multivariate linear regression analysis of factors associated with serum 25(OH)D levels

Term	Estimate	Standard Error	95% Confidence interval	p-value
Age (years)	−0.32	0.15	−0.61, −0.03	0.04
Ethnicity (non-Hispanic white)	2.64	1.06	0.56, 4.72	0.01
Body mass index (non-obese)	2.51	0.91	0.73, 4.29	0.006
Season (non-Summer)	−2.28	0.90	−4.04, −0.52	0.01
Total daily vitamin D intake (in IU)	0.0002	0.001	−0.002, 0.002	0.86