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ORIGINAL ARTICLE

Serum Vitamin D Levels as Biomarkers in Patients with Autoimmune Uveitis and their Possible Correlation with Disease Activity

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ABSTRACT

This study investigated the correlation between serum vitamin D levels and intraocular inflammation in patients with autoimmune uveitis (AIU). We evaluated 67 patients with active and inactive AIU and measured their serum 25-hydroxyvitamin D [25(OH)D] concentration, sun exposure habits, number of relapses, and complications. Of the patients evaluated, 85% had significantly lower vitamin D levels, and patients with active uveitis had lower 25(OH)D levels than those with inactive uveitis. The odds of developing active uveitis decreased by 6% with each 1-unit increase in 25(OH)D. Patients with recurrent active AIU had significantly lower 25(OH)D serum levels than inactive forms, indicating that low vitamin D levels may alter the clinical course of intraocular inflammation in AIU. Additionally, the study found that a higher mean BMI increased the chances of an individual having active uveitis by 14%. These results suggest that serum vitamin D concentration could be a prognostic clinical biomarker in AIU.

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Inflammatory eye diseases represent important causes of blindness and visual impairment worldwide.[1] Uveitis accounts for 10% to 15% of visual impairment in the Western world, with the non-infectious, immune-mediated type being the most commonly observed form in developed countries.[2] In Brazil, uveitis accounts for 15.7% of patients with visual impairment and represents the second most frequent diagnosis in low vision clinics.[3]

In non-infectious uveitis, the pathophysiology likely involves autoimmune aggression mediated by T lymphocyte responses to specific antigens in the uveal tract.[4] Interleukin (IL)-17-producing T cells are directly involved in the pathogenesis of autoimmune diseases and experimental models of uveitis, which suggests the existence of common autoimmune mechanisms.[5] These autoimmune mechanisms lead to uveitis as an ocular manifestation of these underlying systemic diseases.[5] In addition, vitamin D deficiency has been linked to several uveitis-related autoimmune disorders, including spondyloarthritis, inflammatory bowel disease, juvenile idiopathic arthritis, systemic lupus erythematosus, and Sjögren's syndrome.[6–9] This association is robust with multiple sclerosis (MS), where vitamin D potentially prevents MS relapses.[10,11] Importantly, MS and immune-mediated uveitis are closely related experimentally and clinically.[12,13]

The therapeutic potential of vitamin D and its relation to several ocular diseases have motivated scientific studies on its relevance to ocular health, including autoimmune uveitis (AIU). Structures directly related to the action of calcitriol [1,25-dihydroxy-vitamin D (1,25(OH)2D), the main agonist of the vitamin D receptor (VDR)], such as its receptor (VDR), the enzyme 1-alpha-hydroxylase (activation enzyme), and its metabolites, have been identified in ocular tissue.[14] In models of experimental AIU, oral administration of calcitriol was shown to prevent intraocular inflammation, and reverse the disease process by reducing the associated immune responses. While IL-17 production was inhibited by Th17 cells, the effect of calcitriol on dendritic cells inhibited the Th17 response. These findings propose that VDR agonists could potentially be used as therapeutic agents in uveitis.[15] Vitamin D plays an essential role as an immune regulator, in both innate and acquired immunity, by preventing an exaggerated inflammatory process. Therefore, vitamin D controls the expansion and differentiation of pro-inflammatory cells, in addition to reducing cytokine release.[16]

However, there is little evidence of the relationship between serum vitamin D levels in patients with uveitis and its possible effect on the clinical evolution of intraocular inflammation.[17] This study aimed to analyze the relationship between serum vitamin D levels and disease activity in a sample of patients with AIU undergoing treatment at a Brazilian tertiary referral center, considering the need to know the potential effect of vitamin D in patients with autoimmune intraocular inflammation and the scarcity of studies in this area.

Material and methods

Ethical principles

This study was approved by the Clinical Research Ethics Committee of the Federal University of São Paulo

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(UNIFESP; protocol 0173/2019; number 3,273,214) and was conducted in accordance with the Declaration of Helsinki and Resolution 466/12 of the National Health Council, as defined in Brazilian legislation.[18,19] All procedures for this study were performed under strict clinical indications, and patients signed the informed consent form after receiving all appropriate information. The research participants authorized the publication of the data, by signing the "Consent to Publication" form.

Study group

In this descriptive, cross-sectional study, we evaluated 67 adult patients with AIU, of both sexes, aged>18 years, who reported to the uveitis clinic of a tertiary referral center (Department of Ophthalmology, EPM, UNIFESP, São Paulo, Brazil), between July 2019 and December 2021.

Our sample did not include individuals with a neoplastic or non-neoplastic masked syndrome, traumatic uveitis, drug-induced uveitis, and infectious causes of uveitis (excluded by specific laboratory tests). Individuals with any systemic disease or other conditions influencing serum vitamin D levels, such as liver or kidney disease, pregnancy or breastfeeding, smoking, body mass index (BMI) >35 kg/m2, history of excessive alcohol consumption, and concomitant use of potentially interacting drugs, were not included in the study.

Diagnosis and clinical evaluation

We considered data on the type of uveitis according to the primary anatomical site of inflammation, disease progression, and clinical features. The diagnosis of AIU was established based on a complete ophthalmologic evaluation, including the patient's clinical history of current and pre-existing diseases, ocular examination (visual acuity measurement, external ocular examination, biomicroscopy of the anterior and posterior segments, tonometry, and indirect binocular ophthalmoscopy), and complementary general and/or ophthalmologic tests as necessary to confirm the diagnostic hypothesis. patients signed the informed consent form after receiving all appropriate information. After receiving all appropriate information and signing the informed consent form, patients were evaluated for uveitis activity by ophthalmologic exam, and they performed the blood collection sample to 25-hydroxyvitamin D dosage during the same ophthalmologic consultation.

The clinical criteria for the diagnosis and classification of uveitis were based on the Standardized Uveitis Nomenclature (SUN) approved by the International Uveitis Study Group.[20,21] Uveitis was defined as active if the slit-lamp examination revealed uveitis activity within 30 days prior to the serum vitamin D dosage examination. An anatomical subdivision was used in assessing activity: anterior uveitis was defined as active if it had >0.5+ cells in the anterior chamber or 1+ flare, intermediate uveitis as >0.5+ vitreous cells, and posterior uveitis as active chorioretinal inflammation. Disease data, including anatomical description, whether primary or recurrent, presence of an identifiable uveitis syndrome, or any associated systemic disease, were recorded, including dates of presentation and vitamin D collection.

Data collection

In addition to the demographic data, we considered information on the number of relapses, number of episodes of intraocular inflammation in the last year, and treatments performed. Ocular complications associated with uveitis, including cataract, glaucoma, band keratopathy, epiretinal membrane, retinal detachment, and phthisis bulbi, were also collected based on clinical history records.

Because of the latitudinal influence on vitamin D synthesis in the skin, we recorded sun exposure habits and sunscreen use data. All participants belonged to the same climate exposure zone and completed a questionnaire on sun exposure, based on that validated by the Quantitative Assessment of Solar UV Exposure for Vitamin D Synthesis in Australian Adults (AusD) study.[22] Briefly, participants were asked to answer multiple-choice questions about working indoors or outdoors, nighttime or daytime, in the previous month (yes or no); length of time exposed outdoors on each weekday and weekend [never, <15 minutes, 15–30 minutes, 30–45 minutes, 45–60 minutes, or more (specify hours)]; frequency of summer use of hat or cap, long-sleeved shirt, long pants, sunglasses, and sunscreen (never/rarely, less than half the time, more than half the time, almost always); and frequency of vitamin D supplement intake in the past month (none, 1–2 doses per week, one dose per day, more than one dose per day). Since skin pigmentation can influence vitamin D synthesis, we used the Fitzpatrick classification to describe skin phototypes (Fitzpatrick types I and II represent lighter-skinned individuals, Fitzpatrick types III and IV describe those with moderately pigmented skin, and those with higher skin pigmentation were classified in Fitzpatrick types V and VI).[23] Considering BMI as an indicator of appropriate weight, we classified participants with normal BMI, overweight, or obesity, thus targeting the relationship between obesity and a higher risk of hypovitaminosis D.[24,25]

Determination of vitamin D in the blood

Calcidiol, also called calcifediol or 25-hydroxyvitamin D [25(OH)D], the most abundant and stable vitamin D metabolite in serum, was selected for vitamin D analysis.[26] The blood samples to determine serum 25(OH)D concentrations were obtained in a dry tube using venipuncture after 4–6 h of fasting; they were subsequently centrifuged and processed for electrochemiluminescence analysis. We adopted the Endocrine Society Clinical Practice Guideline, which considers 25(OH)D levels 21–29 ng/mL and ≤20 ng/mL as insufficiency and deficiency, respectively; in addition, it recommends levels ≥30 ng/mL, to optimize extra-skeletal actions of D3, such as immunomodulation, which is relevant to our study.[26]

Statistical analysis

Statistical analysis was performed to study the association between uveitis activity and 25(OH)D serum levels (main variable), with sex, age (years), BMI (kg/m^2) and skin phototype (pigmentation) as covariates. Absolute and relative

frequencies were calculated for categorical variables, and mean and standard deviation (MD ± SD) for numeric variables. The statistical technique of univariate and multivariate logistic regression, with a stepwise logistic backward method, was used in the association study, with disease activity (signs of ocular inflammation) as the dependent variable. The Odds Ratio (OR) and respective 95% CI resulting from the univariate and multiple logistic regressions were presented in a single table. We verified the absence of moderate or severe multicollinearity between the independent variables to ensure that a possible association between the independent variables does not interfere with the results of the multiple logistic regression. In addition, we also explored the association between the number of relapses (one or two relapses/year, or ≥ three relapses/year) of the disease and the presence of uveitis complications with 25(OH)D serum levels using the Mann-Withney test (numeric variable is not normally distributed across the comparison groups). The results were presented in the text and a boxplot. All analyses were performed using the Statistical Package for the Social Sciences program, version 18.0, adopting a significance level of 5%.

Results

This study included 67 patients with AIU (70.1% women), with a mean age of 41.6 ± 11.7 years (range 20–66 years), of whom 45 (67%) and 22 (33%) patients had active and inactive uveitis, respectively. None of the participants reported sun exposure for at least 30 min/day; 68.6% ($n = 46$) used sunscreen frequently, and 91% ($n = 61$) worked indoors. According to Fitzpatrick's classification, the predominant skin types in the study group were types IV ($n = 28$, 41.8%) and III ($n = 23$, 34.3%). Only six patients (8.9%) reported vitamin D supplement use, in the month preceding the analysis (data not shown).

Most subjects were overweight ($n = 29$, 43.3%) or obese ($n = 17$, 25.3%), and only 31.3% ($n = 21$) had an appropriate weight (normal BMI). The mean BMI of the participants was 27.5 ± 4.63 (range 19.0–40.8).

The main uveitic syndromes reported were Vogt-Koyanagi-Harada syndrome ($n = 22$, 32.8%) and Behçet's disease ($n = 8$, 11.9%). The most frequent cause of anterior uveitis was ankylosing spondylitis ($n = 6$, 9.0%). The associated systemic diseases were HLA-B27-related (ankylosing spondylitis and psoriatic arthritis), rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease (ulcerative rectocolitis). We considered eight (11.9%) cases of idiopathic etiology. Table 1 presents the primary characteristics of the study groups.

The mean serum 25(OH)D level of the total sample was 23.7 ± 10.2 ng/mL, with 85% ($n = 57$) of UIA patients having lower 25(OH)D levels and only ten individuals (15%) having levels ≥30 ng/ml (Figure 1).

Active uveitis was observed in 55.0% of males and 72.3% of females. Although the frequency of inflammatory activity was higher in females, this association was not statistically significant (OR for females = 2.140; 95% CI 0.721–6.354; $p = 0.171$). The mean age in the groups with and without active uveitis was 40.6 ± 11.6 and 43.4 ± 11.9, respectively. The odds of the individual having uveitis activity do not change with age (OR = 0.980; 95% CI 0.937–1.024; $p = 0.362$), illustrated in Table 2.

The proportion of cases of active uveitis in the skin phototype groups was 53.8% in group II, III; 78.6% in group I; 69.2% in group V, VI. There was no statistically significant association between skin phototype and uveitis activity (Table 2). We can see higher 25(OH)D serum levels in individuals with less pigmented skin phototypes. However, this association was not strong enough to generate multicollinearity problems in the regression model (Table 2).

The mean BMI in the group with and without active uveitis was 28.3 ± 4.57 and 25.8 ± 4.4, respectively. We observed a significantly statistically association between BMI and activity uveitis (OR = 1.140; 95% CI 1.002–1.297; $p = 0.047$). An increase of one unit in BMI increases the chances of an individual having active uveitis by 14% (Table 2). Finally, no multicollinearity was identified. VIF (variance inflation factor) of the variables were: sex 1.067, age (years) 1.033, BMI (Kg/m^2) 1.157, and skin 1.060.

According to Figure 2, the subjects with inactive uveitis had higher 25(OH)D levels than those with active disease, with mean serum 25(OH)D levels of 27.7 ± 11.3 ng/mL and 21.7 ± 9.1 ng/mL, respectively ($p = 0.017$). Considering uveitis activity in the logistic regression model, we observed the probability of developing active uveitis decreased by 6% with each 1-unit increase in 25(OH)D (OR = 0.944, 95% CI 0.894–0.996; $p = 0.034$), meaning that a 10-unit increase in blood 25(OH)D causes a 60% reduction in the risk of active disease (Table 2). Individuals with 25(OH)D levels >20 and <30 ng/ml and 25(OH)D levels ≤20 ng/ml were more likely to have uveitis activity than those with 25(OH)D ≥ 30 ng/mL, with OR = 5.963 (95% CI 1.257–28.281; $p = 0.025$) and OR = 7.4 (95% CI 1.441–37.883; $p = 0.016$), respectively.

Regarding the number of relapses reported in the year preceding the serum 25(OH)D analysis, 24 patients (35.8%) reported <3 episodes, 24 (35.8%) had 3–5 episodes, and 19 (28.3%) had >5 episodes of ocular inflammation. Individuals who reported fewer relapses (one or two episodes of ocular inflammation per year) had higher mean 25-hydroxyvitamin D concentrations (31.6 ± 10.3 ng/mL) than the groups with three or more episodes a year (19.3 ± 7.0 ng/mL), and this difference was statistically significant ($p < 0.001$) (Figure 2).

Finally, we analyzed the group of AIU patients with uveitis complications ($n = 40$, 59.7%) such as secondary cataract, glaucoma, band keratopathy, epiretinal membrane, retinal detachment, or phthisis bulbi. These presented a mean 25(OH)D level (22.8 ± 8.8 ng/mL) lower than the group without complications (25.1 ± 11.9 ng/mL); however, this difference was not statistically significant ($p = 0.808$).

Discussion

We analyzed serum 25(OH)D levels in patients with AIU, with or without intraocular inflammation, according to internationally standardized criteria.[20] The observed serum 25(OH)D levels were significantly lower in those with active disease. These results suggest a possible correlation between hypovitaminosis D and intraocular inflammation, indicating that serum 25-hydroxyvitamin D concentration could be a potential biomarker for this disease. Therefore, its supplementation should be

Table 1. Demographic and clinical characteristics.

Demographic data	Group ($N = 67$)
Age (years); MD ± SD	41.6 ± 11.7
Sex; n (%)	
Females	47 (70.1)
Males	20 (29.9)
Skin phototypes[(a)]; n (%)	
II	3 (4.5)
III	23 (34.3)
IV	28 (41.8)
V	10 (14.9)
VI	3 (4.5)
BMI (Kg/m^2; MD ± SD	27.5 ± 4.6
BMI classification[(b)]; n (%)	
Healthy weight	21 (31.2)
Overweight	29 (43.3)
Obesity	17 (25.4)
25(OH)D serum level (ng/mL); MD ± SD	23.7 ± 10.2
Disease activity[(c)]; n (%)	
Active	45 (67.2)
Inactive	22 (32.8)
Anatomical classification; n (%)	
Anterior	12 (17.9)
Intermediate	13 (19.4)
Posterior	37 (55.2)
Panuveitis	5 (7.4)
Etiology; n (%)	
Vogt-Koyanagi-Harada syndrome	22 (32.8)
Pars planitis & Intermediate uveitis	10 (14.9)
Behçet disease	8 (11.9)
Idiopathic	8 (11.9)
Ankylosing spondylitis	6 (9.0)
Others(d)	13 (19.4)
Total	67 (100)

[(a)]According to reference.[23]
[(b)]According to reference.[24,25]
[(c)]According to SUN criteria, reference.[20,21]
[(d)]Multiple sclerosis, Crohn's disease, rheumatoid arthritis, choroiditis and retinal vasculitis.
BMI, body mass index; 25(OH)D, 25-hydroxy vitamin D; MD, mean; SD, standard deviation.

Table 2. Result of the univariate and multivariate analysis for the association between uveitis activity and the variables age, sex, skin phototype, BMI and serum levels of 25-hydroxyvitamin D.

		Univariate Logistic Regression		Multiple Logistic Regression	
Variable		*p*	OR (CI 95%)	*p*	OR (CI 95%)
Sex	Female	.171	2.140 (0.721–6.354)	-	-
Age (years)		.362	0.980 (0.937–1.024)	-	-
Skin phototypes	II, III	.162	1.000	-	-
	IV	.059	3.143 (0.959–10.302)	-	-
	V, VI	.360	1.929 (0.472–7.881)	-	-
BMI (kg/m^2		*.047*	1.140 (1.002–1.297)	*.027*	1.170 (1.018–1.345)
25(OH)D serum level (ng/mL)		*.034*	0.944 (0.894–0.996)	*.021*	0.931 (0.876–0.989)

BMI, body mass index; 25(OH)D, 25-hydroxy vitamin D.
OR (CI 95%), Odds Ratio and 95% confidence interval.

considered to correct the deficit and favor better clinical outcomes in these patients.

Considering the sufficient 25(OH)D level of 30 ng/mL, as recommended by the American Society of Endocrinology (Endocrine Society), 85% ($n = 57$) of AIU patients had significantly lower 25(OH)D levels, with only ten individuals (15%) having a level considered adequate (≥30 ng/mL). The adopted criteria for serum 25(OH)D levels advocate sufficient metabolic levels based on the increasing clinical evidence of the beneficial properties of serum vitamin D at ≥30 ng/mL.[16,27–30]

Although the association between hypovitaminosis D and an increased risk of AIU has been reported, a causal relationship remains to be elucidated.[17,27,31–37] As in the literature, our study showed a high prevalence of hypovitaminosis D in the AIU group and significantly lower 25(OH)D levels in patients with the active form of the disease, suggesting that higher serum levels of 25(OH)D may favor better control of ocular inflammation, consistent with earlier findings.[17,36,37] The logistic regression model showed the probability of developing active uveitis decreased by 6% with each 1-unit increase in 25(OH)D, meaning that a 10-unit increase in blood 25(OH)D causes a 60% reduction in the risk of active disease. Therefore, the chances of uveitis activity increase as 25(OH)D levels decrease.

Serum 25(OH)D level (ng/mL)*	Active uveitis n (%)	Inactive uveitis n (%)
≥ 30 ng/mL	3 (30.0)	7 (70.0)
> 20 ng/mL and < 30 ng/mL	23 (71.9)	9 (28.1)
≤ 20 ng/mL	19 (76.0)	6 (24.0)
Total	**45** (67.1)	**22** (32.9)

*Recommended 25(OH)D serum levels according to the Endocrine Society (26)

Pearson Chi-Square=7.470 (p = 0.024)

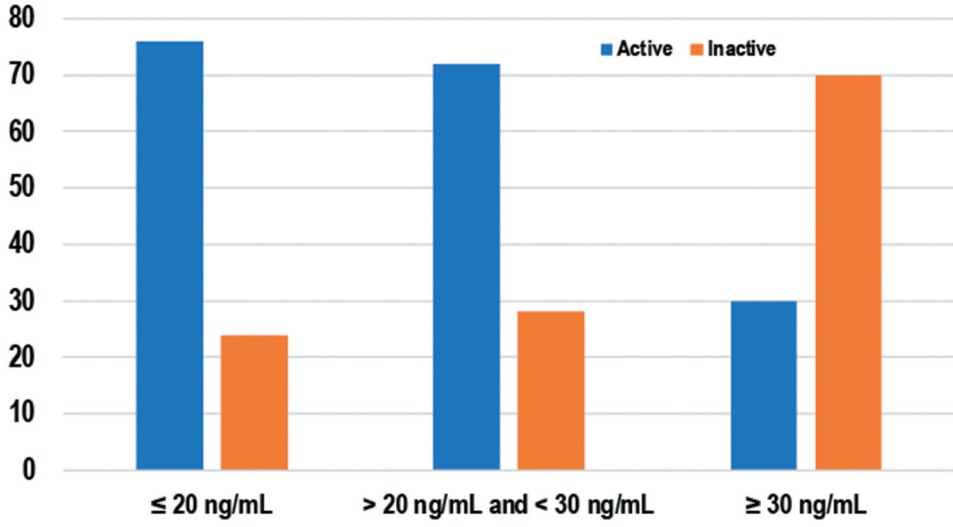

Figure 1. Distribution of patients (%) with active uveitis (signs of ocular inflammation), according to 25(OH)D serum level, considering the recommended levels of the Endocrine Society.

Even though it is known as "vitamin D," calcitriol belongs to the group of fat-soluble prohormones, with significant immunomodulatory effects, in addition to its classic role in calcium and phosphorus metabolism.[38] While it is endogenously produced from the photoisomerization at the epidermis, after exposure to natural ultraviolet B (UVB, 290–370 nm) radiation from sunlight, dietary supplementation is usually insufficient.[38] Thus, the degree of skin pigmentation, dietary habits, currently recommended protection from exposure to sunlight, and indoor work routine can predispose to vitamin D deficiency, defined as a serum level <20 ng/mL (50 nmol/L), even in tropical countries.[39–41] Regarding sun exposure, the participants lived in a low-latitude climatic region (São Paulo, Brazil) and presented common habitual characteristics: a) none of the participants reported a minimum sun exposure of 30 min at least twice a week, b) most carried out their activities indoors, c) most used sunscreen, and d) the majority had moderate to highly pigmented skin type (according to Fitzpatrick's classification). Consistent with earlier reports on the sun exposure patterns and dietary habits in patients with AIU,[17] our results corroborate the evidence that decreased serum levels of 25(OH)D are frequently found in patients with active clinical forms of AIU, despite our study group belonging to a tropical region with a higher solar radiance. In addition, only 8.9% of study participants used vitamin D supplements. Although the objective of the present study was not to assess the association of vitamin D supplementation with a decrease in inflammation or a better clinical course of active forms of this disease, this offers valuable insight for future studies.

Obesity is a risk factor for exacerbating immune-mediated uveitis in experimental and in vivo models.[42,43] Furthermore, 25(OH)D levels are inversely related to body weight.[24,25] In our sample, the mean BMI in the group with active uveitis was higher than those with inactive disease, and this association was statistically significant. An increase of one unit in BMI increases the chances of an individual having active uveitis by 14%, reinforcing the comorbidity aspect of obesity.

We found higher episodes of ocular inflammation in individuals with lower levels of 25(OH)D. Notably, chronic or recurrent uveitis is frequently associated with severe vision loss and ocular morbidity.[20,21] Current treatments for recurrent uveitis, although tentatively effective at reducing inflammation, have potential systemic and ocular side effects.[44] Although very few studies have evaluated the number of relapses in immune-mediated uveitis and its possible correlation with vitamin D levels, there is clinical evidence of the beneficial effect of oral supplementation of 50 000 IU/week for

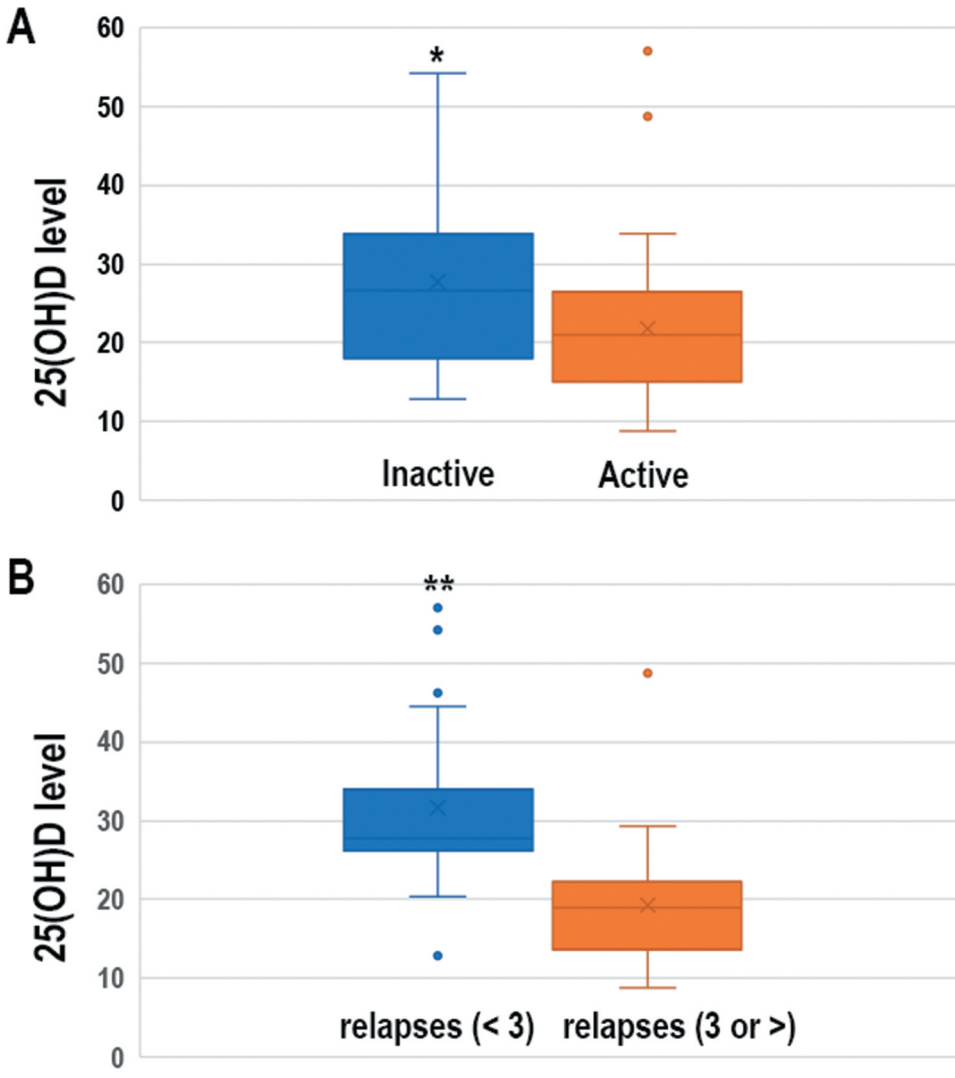

Figure 2. Distribution of serum 25(OH) D levels (ng/mL) in subjects with active and inactive uveitis (A) and in groups with fewer relapses (one or two episodes/year) and more relapses in last year (≥3 episodes/year) (B). *, Mann-Whitney U = 316.500 ($p = 0.017$); **, Mann-Whitney U = 124.5 ($p < 0.001$).

the significant reduction of relapses.[45] In addition, we also found a lower prevalence of ocular complications in patients with higher serum concentrations of 25(OH)D. Considering the improved immunomodulation with more elevated serum 25(OH)D levels, its relationship with uveitis severity needs further investigation. The evaluation must consider vitamin D supplementation as a therapeutic strategy to promote better clinical control and disease prognosis.[16,28,29]

Exploring the association of hypovitaminosis D in autoimmune uveitis, this study has several key strengths. We emphasize that we conducted this study in a specialized uveitis clinic in a tertiary referral center and could perform vitamin testing during uveitis activity or inactivity. To our knowledge, this is the first study to assess vitamin D deficiency in patients with UIA in the Brazilian population. Several clinical correlations have been explained, including those associated with disease activity, recurrence, and an increased risk of the intraocular inflammatory process. Although the present study's design limits the exploration of a causal relationship between the variables, we evaluated some factors that could influence serum vitamin D levels, such as sun exposure, skin type, and overweight status.

Conclusion

In the present study, we observed significantly lower serum vitamin D levels in patients with active AIU compared to those with the inactive type. A similar inverse relationship was observed between serum 25(OH)D levels and the number of relapses of intraocular inflammation. These data suggest that vitamin D deficiency is associated with the clinical course of AIU. Further prospective studies are required to evaluate the efficacy of vitamin D supplementation in such patients. Our results also suggest that serum 25(OH)D levels in patients with AIU could serve as a clinical biomarker, and correcting its deficiency may contribute to better control of intraocular inflammation.

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No potential conflict of interest was reported by the author(s).

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