Association of hypovitaminosis D with Systemic Lupus Erythematosus and inflammation

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Abstract

Introduction: Nowadays it is described a high prevalence of hypovitaminosis D in Systemic Lupus Erythematosus (SLE), which is associated with some clinical manifestations and increased inflammatory activity. **Objective:** To evaluate the association between vitamin D insufficiency with SLE and inflammatory markers. **Methods:** Cross-sectional study, in which have been evaluated 45 SLE patients and 24 controls without the disease. Levels of 25-hydroxyvitamin D [25(OH) D] less than 30 ng/mL were considered inadequate. Disease activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). High sensitivity C reactive protein (hsCRP) and interleukin-6 (IL-6) were evaluated for verification of the inflammatory status. For assessment of renal involvement, analysis of abnormal elements and urinay sediment (AES), quantitative hematuria and pyuria, proteinuria and creatinine clearance in 24-hour urine and serum anti-double stranded DNA were performed. **Results:** The prevalence of 25(OH)D insufficiency was 55% in SLE patients and 8% in the controls participants (p = 0.001). The median of 25(OH)D was lower in patients than in controls. Patients with insufficient 25(OH)D had higher levels of IL-6 and higher prevalence of hematuria in the AES. There was no correlation between vitamin D and SLEDAI or lupus nephritis. **Conclusion:** In our study, vitamin D deficiency was more prevalent in patients with SLE and was associated with higher levels of IL-6 and hematuria.

Keywords: inflammation; lupus nephritis; lupus erythematosus, systemic; vitamin D.

Introduction

Systemic lupus erythematosus (SLE) is a multi-system chronic inflammatory disease that primarily affects young women of reproductive age, at a ratio of nine women for every man.[1] Prevalence ranges from 20 to 150 cases/100,000 individuals.[2] The etiology of SLE is still obscure, and its progression apparently involves the interaction of genetic, hormonal, environmental, and immune factors.[3]

Renal involvement is still one of the determining factors in patient morbidity and mortality, with symptoms manifesting in 50% to 70% of the cases, although electron microscopy (EM) images reveal kidney disease in every patient with SLE. Renal manifestations usually appear within the first two to five years of disease.[4]

Vitamin D deficiency, now recognized as an epidemic, may be an environmental factor in the triggering of SLE.[5] Vitamin D has a direct role in the regulation of bone homeostasis;[6] however, evidence indicates its pluripotent effect is exerted on various organs and systems, one of them being the immune system.[7] In the immune system, vitamin D boosts innate immunity and suppresses

adaptive immunity; it indirectly affects T-cell polarization and shifts the immune response toward tolerance.[8] Its effect on B cells inhibits the secretion of antibodies and the production of autoantibodies.[9]

Several studies have reported a high prevalence of vitamin D deficiency in individuals with autoimmune diseases, SLE included.[10-13] Additionally, 25-hydroxy vitamin D deficiency has been associated with nephritis and severity of disease in patients with SLE.[14]

Few studies have looked into SLE and vitamin D in Brazil. This study aimed to assess the association between vitamin D insufficiency, SLE, and inflammation.

Methods

The sample

The authors of this cross-sectional study reviewed the medical charts of SLE patients seen at the Rheumatology Clinic in the Health Care Center of the Hospital of the Federal University of Juiz de Fora (CAS/HU-UFJF). One hundred and twenty-six eligible patients were invited to join the study, and 45 accepted the invitation and were enrolled. Twenty-four healthy individuals (with no signs of disease on clinical examination or workup) paired for gender and age, residing in the same area, students of medicine at UFJF and nursing at Estacio de Sá University in Juiz de Fora, were included in the control group.

Enrollment criteria

The study included patients aged 18 years and older, diagnosed with SLE according to the criteria of the American College of Rheumatology (ACR) published in 1982 and revised in 1997.[15,16] Patients were asked to give informed consent before joining the study.

Exclusion criteria

Pregnant women, individuals with systemic diseases that lead to renal involvement such as *diabetes mellitus*, vasculitis, acute infectious diseases, viral hepatitis B and C, and the Acquired Immunodeficiency Syndrome (AIDS) were not included in the study.

Methodology

Data collection took place from May of 2010 to March of 2011. The study was approved by the Research Ethics Committee of the UFJF Hospital. The patients and controls who agreed to join the study completed a structured questionnaire addressing the following clinical variables: age, gender, self-reported race, exposure to sunlight (hours/week), the season in which the questionnaire was answered, use of sunscreen, and smoking.

Patients on calcium and vitamin D pills stayed off their drugs for six weeks (three times the half-life of the medication) before joining the study.

Disease activity and inflammation

Disease activity was evaluated through the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Inflammation status was assessed by serum analyses of us-CRP (turbidimetry) and IL-6 (competitive enzyme-linked immunoassay - ELISA).

Lupus nephritis

This study adopted the criteria for lupus nephritis described by the ACR.[16] Patient submitted to renal biopsies were categorized based on the classification for glomerulonephritis in SLE of the WHO published in 1989 and revised in 2004.[17] The workup for renal involvement included urinalysis, quantitative hematuria and pyuria, 24-hour urine proteinuria and creatinine clearance, and serum anti-native DNA.

Vitamin D

Serum levels of 25-hydroxy vitamin D were established by high performance liquid chromatography (HPLC) tests run in a Shimadzu system (Tokyo, Japan). Patients were considered to have sufficient levels when 25(OH)D ≥ 30 ng/mL, insufficient when levels were between 15 and 29 ng/mL, and deficient when levels were < 15 ng/mL.[7]

Statistical analysis

The subjects included in the study were chosen by convenience sampling. The Shapiro-Wilk

test was used to assess the normality of the data set. The mean and median values of continuous variables were used in descriptive statistics. Absolute and relative frequencies were used for categorical variables. The Mann-Whitney U test was used to assess the differences between the ordinal and interval variables of the case and control groups. Differences between nominal variables of both groups were analyzed using the chi-square test. The correlation between 25(OH) D and the variables used to assess nephritis, disease activity, and inflammation was calculated using Pearson's correlation coefficient.

The Kruskal-Wallis test was used to compare the data from subgroups of patients with sufficient and insufficient levels of vitamin D to control group data sets.

Statistical significance was attributed to p-values < 0.05. Statistical analysis was performed on software package SPSS (Statistical Package for Social Sciences) Inc, Chicago, IL, USA, version 19.0.

Results

Tables 1 and 2 show the baseline clinical characteristics and workup data of patients and controls.

The median serum level of 25(OH)D was lower in patients with SLE (29.48 ng/mL, ranging from 20.83 to 44.23 ng/mL) than in controls (37.68 ng/mL, ranging from 22.91 to 44.07 ng/ml) (p = 0.001). The prevalence of insufficient levels of 25(OH)D was higher in patients with SLE (55%) than in controls (8%) (p = 0.001).

Twenty patients (44.4%) were categorized as having lupus nephritis according to the ACR criteria. Eight (44%) of them had renal biopsies done and five (62.5%) were diagnosed with stage-4 disease according to the WHO criteria. The patients in the nephritis subgroup had a mean age of 34.9 ± 7.3 (22-50 years), a mean SLEDAI score of 10 (0-24), IL-6 levels ranging from 0.9 to 13.5 in a median of 5.0 pg/mL, and us-CRP between 0.5 to 36.2 with a median of 4.8 mg/L. The mean serum creatinine level was 0.8 (0.5-2.6) mg/dL and the mean creatinine clearance was 43.9 (35.6-220) mL/min/1.73 m^2. Proteinuria ranged from 112 to 4000, with a median of 946 mg/24 hours. Vitamin D levels ranged from 20.8 to 44.2 with a median of 29.5 ng/mL. No differences were seen between the vitamin D levels of patients with SLE and nephritis *versus* patients with SLE without nephritis.

The prevalence of proteinuria measured by dipstick was significantly higher in the patients in the SLE group when compared to the individuals in the control group [16 (35.6%) and 1 (4.0%), p = 0.012]. The median 24-hour proteinuria was statistically higher in the group of patients with SLE when compared to controls [234 (1-4000) mg/24 hours and 105.5 (47.5 to 189.5) mg/24 hours, p = 0.003]. No statistically significant differences were seen between serum creatinine [0.7 (0.5-2.6) mg/dL and 0.7 (0.5-1.0) mg/dL, p = 0.182] and creatinine clearance [101.1 (34-220) ml/min/1.73 m^2 and 107.6 (60 to 232.7) ml/min/1.73 m^2 (p = 0.258)] levels of the patient and control groups.

Patients with vitamin D deficiency had a higher prevalence of hematuria in urinalysis than patients with sufficient levels of vitamin D and controls [10 (40.0%), 3 (15.0%), and 3 (12.5%) (p = 0.043)], respectively.

The analysis of SLEDAI scores revealed that 64.4% (n = 29) of the patients had active disease (SLEDAI ≥ 6). The median SLEDAI score was 10 (0-24) (Table 2).

IL-6 levels were higher in the group with vitamin D insufficiency [4.464 pg/mL (1.021 to 52.049)] than in the group with sufficient levels of vitamin D [3.292 pg/mL (0.898 to 10.447)] and in the control group [1.386 pg/ml (0.820 to 6.934)] (p < 0.0001) (Figure 1). No differences were observed with respect to us-CRP levels.

Bivariate analysis showed weak evidence of an inverse correlation between vitamin D and IL-6 (r = -0.276, p = 0.066). No correlations were observed between vitamin D and the other variables used to assess disease activity and lupus nephritis.

Discussion

This study showed a higher prevalence of vitamin D insufficiency in patients with SLE, and an association between vitamin D insufficiency and higher levels of IL-6.

Table 1 Group clinical, demographic, and workup characteristics

	Patients (n = 45)	Controls (n = 24)	*p* value
Age (years)	35.3 (20-52)	26 (18-53)	NS
Gender			NS
Male	1 (2.2%)	1 (4.0%)	
Female	44 (97.8%)	24 (96.0%)	
Race			< 0.0001
White	21 (46.7%)	22 (88.0%)	
Non-white	24 (53.3%)	3 (12.0%)	
Season	13 (28.88%)	1 (4.0%)	NS
Fall	20 (44.44%)	0 (0.0%)	
Winter	7 (15.56%)	10 (40.0%)	
Spring	5 (11.11%)	14 (56.0%)	
Summer			
Exposure to sunlight (hours/week)			0.002
< 1	16 (35.5%)	2 (8.0%)	
1 a 2	12 (26.7%)	2 (8.0%)	
3 a 4	6 (13.3%)	4 (16.0%)	
4 a 5	1 (2.2%)	5 (20.0%)	
> 5	10 (22.2%)	12 (48.0%)	
Use of sunscreen			NS
No	7 (15.66%)	9 (36.0%)	
Yes	38 (84.44%)	16 (64.0%)	
Number of sunscreen applications			NS
0	7 (15.6%)	9 (36.0%)	
1	22 (48.9%)	9 (36.0%)	
2	8 (17.8%)	5 (20.0%)	
> 2	8 (17.8%)	2 (8.0%)	
Smoking			0.048
No	38 (84.4%)	24 (96.0%)	
Yes	7 (15.6%)	1 (4.0%)	
ESR 1st hour (mm)	36 (2-173)	15 (3-42)	< 0.0001
Us-CRP (mg/L)	4.9 (0.4-67.9)	2.5 (0.1-11.3)	0.002
C3 (mg/dL)	156.9 (80.8-301.7)	NA	NA
C4 (mg/dL)	25.8 (10.2-67.0)	NA	NA
IL-6 (pg/mL)	3.81 (0.898-52.049)	1.38 (0.820-6.934)	< 0.0001
Total calcium (mg/dL)	9.6 (8.1-11.3)	10.4 (8.5-11.1)	0.015
Phosphorus (mg/dL)	3.9 (2.4-5.3)	3.8 (2.8-4.8)	NS
Intact PTH (pg/mL)	44.9 (6.5-545.9)	35.4 (19.0-80.7)	NS
25(OH)D (ng/mL)	29.48 (20.83-44.23)	37.68 (22.91-44.07)	< 0.0001
Creatinine clearance (mL/min/1.73 m^2)	101.1 (34-220)	107.6 (60-232.7)	NS
Proteinuria (mg/24 hours)	234 (1-4.000)	105.5 (47.5-189.5)	0.003
Hematuria	13 (28.9%)	3 (12.5%)	NS

Data in the form of median value (minimum and maximum) or n (%); NA: Not applicable; NS: Not significant.

Table 2 Patient baseline clinical characteristics

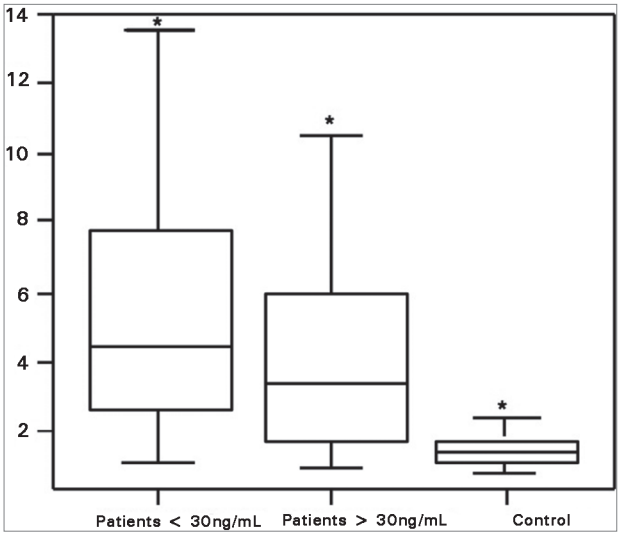
	Patients (n = 45)
Tempo de duração (meses)	72 (3-264)
SLEDAI	10 (0-24)
SLEDAI	29 (64.4%)
Disease activity (≥ 6)	
Use of steroids	42 (93.3%)
Steroid dose (mg of prednisone)	20 (0-60)
Calcium/vitamin D	8 (12.0%)
Antimalarial medication	34 (75.55%)
Chloroquine diphosphate 250 mg/day	22 (48.9%)
Hydroxychloroquine 400 mg/day	12 (26.7%)
Immunosuppressants	25 (55.55%)
Azathioprine	17 (37.8%)
Mycophenolate mofetil	1 (2.2%)
Cyclophosphamide	3 (6.7%)
Methylprednisolone + cyclophosphamide	1 (2.2%)
Rituximab	1 (2.2%)
Methylprednisolone	1 (2.2%)
Methotrexate	2 (4.4%)

Descriptive analysis: median (minimum-maximum) for continuous variables and n (%) for categorical variables.

Vitamin D deficiency is highly prevalent among patients with SLE from all over the world.[18,19] Low levels of vitamin D have also been reported for the Brazilian population, even in healthy individuals.[20,21] The results of this study - carried out in the city of Juiz de Fora, located on latitude 21°45" south - revealed a high prevalence of insufficient levels of vitamin D in patients with SLE when compared to controls, as also reported by Fragoso *et al.*[10] in a study conducted in the Brazilian northeastern state of Pernambuco, in which vitamin D insufficiency was seen in 57.7% of 78 patients with SLE. Three other Brazilian studies support our findings.[11-13]

In our study, no correlations were seen between vitamin D and the variables used to assess lupus nephritis. Higher prevalence of hematuria was seen in patients with vitamin D insufficiency when compared to groups with sufficient vitamin D levels and controls. Most patients had controlled kidney disease, which may have influenced the analysis of results. Lupus nephritis constitutes a major cause of morbidity and mortality in SLE. The association between vitamin D deficiency and lupus nephritis has been

Figure 1. Insufficient levels of vitamin D and IL-6 in SLE - Box-plots for variables IL-6 (pg/mL) for patients with insufficient [4.464 pg/mL (1.021- 52.049)] and sufficient levels of vitamin D [3.292 pg/mL (0.898-10.447)]; and controls [1.386 pg/mL (0.820- 6.934)] (p < 0.0001). Kruskal-Wallis test, $p < 0.05$.



evaluated in studies such as the one published by Kamen *et al.*,[22] in which an association between vitamin D deficiency and nephritis was described. Robinson *et al.*[23] studied patients with juvenile SLE and observed an inverse association between serum levels of 25(OH)D and protein/creatinine ratios, in addition to lower levels of vitamin D in patients with proteinuria.

Although some authors have described a correlation between vitamin D and markers of renal disease activity, our results did not support such finding. An Iranian study with patients with SLE found that the subjects with levels of 25(OH)D lower than 5 ng/mL had higher titers of anti-native DNA.[24] An inverse association between 25(OH)D levels and anti-native DNA (r = -0.13, p = 0.02) and anti-C1q (r = -0.14, p = 0.02) levels was also observed in a recent study by Mok *et al.*[25]

A recent study by Petri *et al.*[14] described significant improvements in protein/creatinine ratios after vitamin D supplementation was offered to patients with insufficient levels of 25(OH)D.

SLE - by definition an autoimmune inflammatory disease - exacerbates inflammation in patients suffering from this condition. In our study, significant increases in us-CRP and IL-6 were observed in patients when compared to controls. Considering specifically the relationship between 25(OH)D and IL-6, significantly higher levels of the cytokine were seen in patients with

vitamin D insufficiency when compared to patients with sufficient levels of vitamin D and controls. Weak evidence of an inverse association between vitamin D and IL-6 was observed in the assessed patients (r = -0.276, p = 0.066). As previously mentioned, these results may be a reflection of the low level of disease activity seen in the evaluated patients, most of whom had mild disease.

As also seen in our findings, Amezcua-Guerra *et al.*[26] and Chun *et al.*[27] described a positive association between SLEDAI scores and ESR/CRP in patients with SLE. However, Firooz *et al.*[28] failed to show an association between these markers of inflammation and disease activity. IL-6 influences the regulation of the immune system and inflammation, acting in the differentiation of B and T cells.[29] Patients with SLE have increased levels of various inflammatory cytokines, including IL-6, IL-1, and TNF-alpha,[27,30,31] as reinforced by our findings.

Our study faces a few limitations. As it is a cross-sectional study, causality cannot be suggested between the described associations and the occurrence of vitamin D deficiency in subjects with SLE. The number of enrolled patients (n = 45) may have also impacted the results, as well as their low levels of disease activity. Future studies enrolling a larger number of patients with more severe disease could potentially provide more robust results with regard to the association between insufficient levels of vitamin D, nephritis, inflammation, and disease activity.

Conclusion

The patients with SLE enrolled in this study showed an association between insufficient levels of vitamin D and higher levels of IL-6 and hematuria. No significant correlation was observed between vitamin D levels, lupus nephritis, and SLEDAI scores. More randomized trials are needed to evaluate the impact of vitamin D on SLE, as well as to establish the levels of vitamin D needed to produce effects on the immunomodulation of these patients.

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