SOCIEDADE BRASILEIRA DE REUMATOLOGIA

REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

Original article

On lupus, vitamin D and leukopenia

*Juliana A. Simioni, Flavia Heimovski, Thelma L. Skare**

Rheumatology Unit, Hospital Universitário Evangélico de Curitiba, Curitiba, PR, Brazil

ARTICLE INFO

Article history:
Received 7 October 2014
Accepted 24 June 2015
Available online 4 September 2015

Keywords:
Systemic lupus erythematosus
Vitamin D
Leukopenia
Granulocytopenia

ABSTRACT

Background: Immune regulation is among the noncalcemic effects of vitamin D. So, this vitamin may play a role in autoimmune diseases such as systemic lupus erythematosus (SLE).
Objectives: To study the prevalence of vitamin D deficiency in SLE and its association with clinical, serological and treatment profile as well as with disease activity.
Methods: Serum OH vitamin D3 levels were measured in 153 SLE patients and 85 controls. Data on clinical, serological and treatment profile of lupus patients were obtained through chart review. Blood cell count and SLEDAI (SLE disease activity index) were measured simultaneously with vitamin D determination.
Results: SLE patients have lower levels of vitamin D than controls ($p = 0.03$). In univariate analysis serum vitamin D was associated with leukopenia ($p = 0.02$), use of cyclophosphamide ($p = 0.007$) and methotrexate ($p = 0.03$). A negative correlation was verified with prednisone dose ($p = 0.003$). No association was found with disease activity measured by SLEDAI ($p = 0.88$). In a multiple regression study only leukopenia remained as an independent association ($B = 4.04$; $p = 0.02$). A negative correlation of serum vitamin level with granulocyte ($p = 0.01$) was also found, but not with lymphocyte count ($p = 0.33$).
Conclusion: SLE patients have more deficiency of vitamin D than controls. This deficiency is not associated with disease activity but with leucopenia (granulocytopenia).

Acerca de lúpus, vitamina D e leucopenia

Palavras-chave:
Lúpus eritematoso sistêmico
Vitamina D
Leucopenia
Granulocitopenia

RESUMO

Introdução: A regulação imune está entre os efeitos não calcêmicos da vitamina D. Assim, essa vitamina pode influenciar em doenças autoimunes, como o lúpus eritematoso sistêmico (LES).
Objetivos: Estudar a prevalência da deficiência de vitamina D no LES e sua associação com o perfil clínico, sorológico e de tratamento, bem como com a atividade da doença.
Métodos: Mensuraram-se os níveis séricos de OH-vitamina D3 em 153 pacientes com LES e 85 controles. Os dados sobre o perfil clínico, sorológico e de tratamento de pacientes com

* *Corresponding author.*
E-mail: tskare@onda.com.br (T.L. Skare).
http://dx.doi.org/10.1016/j.rbre.2015.08.008

lúpus foram obtidos por meio da revisão de prontuários. Simultaneamente à determinação da vitamina D, foi feito um hemograma e foi aplicado o Sledai (SLE disease activity índex [índice de atividade da doença no LES]).

Resultados: Os pacientes com LES tinham níveis mais baixos de vitamina D do que os controles (p = 0,03). Na análise univariada, a vitamina D sérica esteve associada à leucopenia (p = 0,02) e ao uso de ciclofosfamida (p = 0,007) e metotrexato (p = 0,03). Foi verificada uma correlação negativa com a dose de prednisona (p = 0,003). Não foi encontrada associação com a atividade da doença medida pelo Sledai (p = 0,88). Em um estudo de regressão múltipla, somente a leucopenia permaneceu como uma associação independente (B = 4,04; p = 0,02). Também foi encontrada correlação negativa do nível sérico de vitamina D com os granulócitos (p = 0,01), mas não com a contagem de linfócitos (p = 0,33).

Conclusão: Os pacientes com LES têm mais deficiência de vitamina D do que os controles. Essa deficiência não está associada com a atividade da doença, mas com a leucopenia (granulocitopenia).

Introduction

Vitamin D has immune modulatory properties.[1] The main source of vitamin for humans is the conversion of 7-dehydrocholesterol in pre vitamin D3 in the skin, which occurs by exposure to ultraviolet radiation.[2] A small portion comes from the diet, mainly seafood 17. Vitamin D3 must first undergo one hydroxylation in the liver resulting in 25 OH vitamin D3 or calcidiol[2] which is the circulating form of the vitamin and that it was the form used for serum measurement at present. The most active form of vitamin D is 1,25 (OH)2 vitamin D synthesized in the kidney.[2] It is known that this vitamin plays an inhibitory role of dendritic cells, CD4, CD8, B lymphocytes and the production of cytokines, such as IFN γ, IL-2, IL-6, TNF-α, and increases the number of T regulatory cells and synthesis of other cytokines such as IL-4, IL-10 and TGF β.[1,3,4] Thus it is conceivable that serum vitamin D levels exert influence on autoimmune diseases such as SLE. However existing studies in this area are contradictory. Birmingham et al.[5] reported that patients with acute disease flare have lower levels of vitamin D but a cause-effect relationship could not be established. Others noted that deficiency of vitamin D has been associated with increased disease activity,[6–8] while others denied it.[4,9,10] Some clinical manifestations have been associated with vitamin D levels such as leukopenia[4] renal involvement,[4] photosensitivity and the presence of anti-ds DNA.[7]

The vitamin D receptor gene polymorphism has been linked with SLE susceptibility in Asian, Polish and Egyptian patients.[11–13] In Brazilians this association could not be demonstrated although it seemed to influence the appearance of cutaneous and articular manifestations and in the presence of anti-ds DNA.[14]

Some factors contribute to a higher prevalence of vitamin D deficiency in SLE patients than in the general population. The photoprotection, held as part of the disease treatment, can block the synthesis of cholecalciferol induced by UVB radiation on the skin.[15] Antimalarials, widely used in this disease, are described by some authors to be associated with its deficiency due to its photoprotective effect.[16] Others believe that this medication hinders the production of dihydroxyvitamin D as they inhibit the alpha-hydroxylase enzyme responsible for transformation of mono in dihydroxyvitamin D.[17] This action could increase circulating levels of the level of monohidroxy vitamin D3 in detriment of dyhidroxy active form.[17]

In the present study we aimed to determine whether the levels of vitamin D in a Southern Brazilian population with SLE are associated with disease activity, serological, clinical profile and with medications used for treatment.

Methods

This study was approved by the local Ethics Committee in Research and all participants signed an informed consent. One hundred and fifty three patients with at least 4 of 1997 modified American College of Rheumatology (ACR) classification criteria for SLE[18] were invited to participate during the period of six months, according to the order of consultation in the clinic and willingness to participate in the study. We excluded patients using anticonvulsants with creatinine greater than 1.3 mg/dL and pregnant women. None of the included patients had made replacement of vitamin D in the last year and none made use of more than 600 IU of vitamin D3/day, which is routinely done in the service for all glucocorticoids users. Demographic, clinical and serological data were collected through chart review. Clinical data were considered a cumulative way and defined according to the 1997 ACR classification criteria for SLE.[18] Disease activity was calculated by SLEDAI (or SLE Disease activity index).[19] Also, data on creatinine levels and blood cell count were collected simultaneously with vitamin D as well as the drugs considered for study were those used at the moment of vitamin D determination.

As controls, we included 85 self-reported healthy individuals from the same geographical area, matched for age and gender.

The serum vitamin D (25 OH vitamin D3) was analyzed by chemiluminescence by the Liaisom 25OH Vitamin D Assay (DiaSorin Inc., Stillwater, MN, USA). Value ≥30 mg/dL were

considered normal; between 20 and 29 mg/dL were considered as vitamin insufficiency and values below 20 mg/dL as deficiency.

Data were collected on the frequency and contingency tables. Study of data distribution was performed by the Kolmogorov–Smirnov test and central tendency was expressed as median and interquartile range (IQR) for non-parametric and mean and standard deviation for parametric data. Association studies of vitamin D levels with clinical, serological and demographic variables were made by Fisher's and chi-square when data was nominal and for unpaired t test when nominal. Correlation studies of SLEDAI values, age, prednisone dose, granulocyte and lymphocyte blood count with values of serum vitamin D were done using Pearson and Spearman test. All variables with $p < 0.1$ in univariate analyze were further studied through multiple linear regression to access its independency. Calculations were made with help of software Medcalc version 12.1.3.0 and the significance was set at 5%.

Results

Description of the studied sample

In the sample of 153 patients with SLE, 11/153 (7.1%) were men and 142/153 (92.8%) were women aged 19–65 years (median 42 years, IQR = 31–49) and disease duration from 6 to 244 months (median 36 months; IQR = 12–72). The SLEDAI values ranged from 0 to 20 (median 0, IQR = 0–2). About 43/126 (34.1%) were smokers. Patients' clinical, serological and treatment profile is seen in Table 1.

In this sample the levels of serum vitamin D ranged from 4.0 to 57.2 (mean 22.5 ± 9.2). In 29/153 (18.9%) patients the values were normal; in 59/153 (38.5%) were insufficient and 65/153 (42.4%) were deficient. In 125/153 (81.6%) had values below the normal range.

The 85 included controls had mean age 41.8 ± 16.4 years; 9/85 were men and 76/85 women and they were matched for age ($p = 0.49$) and gender ($p = 0.36$) with patients. The comparison between the levels of vitamine D between SLE patients and controls can be seen in Fig. 1.

Vitamin D in SLE population according to demographic, clinical, serological and treatment variables

The values of serum vitamin D levels according to studied variables are seen in Table 2.

The correlation of vitamin D levels with prednisone dose showed a negative value with rho = −0.23 (95% CI = −0.38 to −0.07; $p = 0.003$) and a trend was observed with patients age with rho = 0:07 (95% CI = −0.08 to 0.23, $p = 0.360$). No correlation between vitamin D levels and SLEDAI was found (rho = −0.01, 95% CI = 0.15 to −0.17; $p = 0.88$).

When variables with $p < 0.1$ in univariate analysis were studied by multiple linear regression (prednisone, cyclophosphamide, methotrexate, leukopenia, anti Sm and Lupus anticoagulant) only leukopenia remained as an independent variable ($B = 4.04$; $p = 0.02$).

Table 1 – Clinical, serological and treatment profile of 153 patients with systemic lupus erythematous.

	n	
Arthritis	86/140	61.4%
Serositis	34/105	32.3%
Hemolytic anemia	12/139	8.6%
Leukopenia	40/139	28.7%
Thrombocytopenia	35/136	25.7%
Glomerulonephrites	60/140	42.8%
Discoid lesions	15/136	11.0%
Malar rash	72/134	53.7%
Photossensitivity	103/148	69.5%
Oral ulcers	55/138	39.8%
Seizures	17/137	12.4%
Psychosis	9/96	9.3%
Anti Ro	53/137	38.6%
Anti La	25/136	18.3%
Anti Sm	37/132	28.0%
Anti ds DNA	48/136	35.9%
Anti cardiolipin IgG	18/136	13.2%
Anti cardiolipin IgM	17/136	12.5%
Lupus anticoagulante	14/118	11.7%
Azathioprine use	29/145	20%
Methotrexate use	22/145	15.5%
Mophetyl mycophenolate use	17/145	11.7%
Cyclophosphamide use	11/145	7.5%
Antimalarial use	124/153	81.0%
Prednisone use	84/153	37.9%
	Dosage 5–60 mg/day; median = 10 (IQR = 5.0–27.5)	
Creatinine level (mg/dL)	0.5–1.3 (0.77 ± 0.18)	
Hematocrit (%)	23.8–52.8 (39.8 ± 4.27)	
Platellet Platelet (/mm^3)	570,000–534,000 (236,600 ± 74,641)	
Total leukocyte (/mm^3)	1720–17,800 (6431 ± 2907)	
Lymphocyte (/mm^3)	401–4913 (1719 ± 874)	
Granulocyte (/mm^3)	688–14,418 (4712 ± 2365)	

IQR, interquartile range.

Study of leukopenia with serum levels of vitamin D

The study of vitamin D levels and leukocyte cell count showed no correlation of lymphocyte count with serum vitamin D

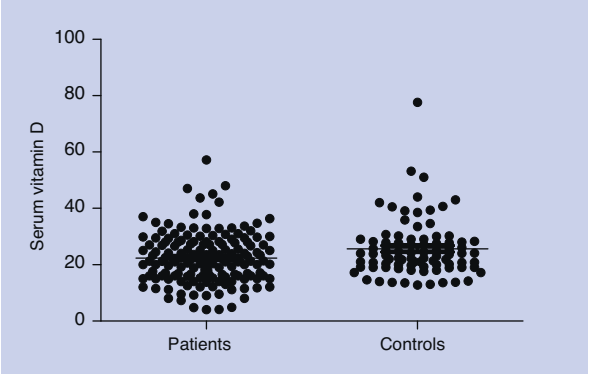

Fig. 1 – Vitamin D levels in systemic lupus erythematosus patients (mean value 22.4 ± 9.16 mg/dLand controls (mean value 25.6 ± 10.2 mg/dL) with $p = 0.03$.

Table 2 – Comparison of vitamin D serum levels according to clinical demographic, serological and treatment variables.

	Serum vitamin D (mg/dL) mean ± SD (range) (with the studied variable)	Serum vitamin D (mg/dL) mean ± SD (range) (without the studied variable)	*p*
Gender (female)	22.59 ± 9.27 (4.1–57.2)	20.15 ± 7.10 (4.0–30.10)	0.39
Tobbaco use	22.30 ± 8.28 (4.1–45.1)	22.46 ± 9.52 (4.0–57.2)	0.92
Artrite	23.4 ± 9.7 (4.1–57.2)	21.8 ± 8.5 (4.0–47.0)	0.32
Serositis	20.8 ± 7.3(9.5–36.4)	23.04 ± 9.5 (4.0–57.2)	0.21
Hemolytic anemia	22.57 ± 8.9 (4.8–42.2)	22.51 ± 8.9 (4.0–57.2)	0.98
Leukopenia	21.4 ± 8.2 (4.0–45.1)	25.2 ± 10.3 (4.1–57.2)	0.02
Thrombocytopenia	22.03 ± 9.197 (4.1–45.1)	22.6 ± 9.2 (4.0–57.2)	0.73
Glomerulonephritis	21.95 ± 9.48 (4.0–48.0)	22.77 ± 9.12 (4.1–57.2)	0.60
Discoid lesions	22.55 ± 7.62 (4.1–33.0)	22.49 ± 9.40 (4.0–57.2)	0.98
Malar rash	21.70 ± 7.92 (8.0–47.0)	23.21 ± 10.23 (4.0–57.2)	0.31
Photossensitivity	22.16 ± 8.69 (4.1–48.0)	23.2 ± 10.28 (4.0–57.2)	0.51
Oral ulcers	23.21 ± 9.25 (4.9–57.2)	22.10 ± 9.22 (4.0–48.0)	0.47
Seizures	21.37 ± 8.69 (11.1–43.7)	22.64 ± 9.30 (4.0–57.2)	0.59
Psychosis	21.92 ± 7.98 (9.5–37.0)	22.54 ± 9.31 (4.0–57.2)	0.84
Anti Ro	21.89 ± 8.39 (4.8–48.0)	23.65 ± 10.59 (4.0–57.2)	0.26
Anti La	24.62 ± 11.76 (4.0–57.2)	22.09 ± 8.63 (4.83–48.0)	0.21
Anti Sm	24.81 ± 11.1 (4.8–57.2)	21.76 ± 8.45 (4.0–48.0)	0.07
Anti dsDna	23.18 ± 8.32 (4.9–45.1)	22.19 ± 9.62 (4.0–57.2)	0.53
Anti RNP	22.13 ± 9.81 (8.0–57.2)	22.63 ± 9.04 (4.0–48.0)	0.77
Anticardiolipin IgG	21.92 ± 2.90 (4.1–57.2)	22.58 ± 8.78 (4.0–48.0)	0.48
Anticardiolipin IgM	19.8 ± 6.9 (4.8–37.0)	22.9 ± 9.32 (4.0–57.2)	0.18
Lupus anticoagulante	18.2 ± 8.24 (4.9–33.7)	23.15 ± 8.93 (4.1–57.2)	0.06
Antimalarial use	22.66 ± 9.38 (4.0–57.2)	21.78 ± 8.54 (4.9–48.0	0.64
Azathioprine use	20.05 ± 8.81 (4.8–37.0)	23.07 ± 9.25 (4.0–57.2)	0.11
Methotrexate use	26.53 ± 8.08 (12.1–47.0)	21.87 ± 9.36 (4.0–57.2)	0.03
Mophetyl mycophenolate use	21.71 ± 9.70 (7.30–42.20)	22.50 ± 9.13 (4.0–57.2)	0.73
Cyclophosphamid use	15.28 ± 7.53 (4.0–33.0)	22.92 ± 9.07 (4.1–57.2)	0.007

levels (rho = 0.07; 95% CI = −0.07 to 0.22; $p = 0.33$). The association study with granulocyte count is on Fig. 2.

Discussion

The result of the present study confirms the findings of other authors, showing that low levels of vitamin D are more common in lupus patients than in the normal population from the same geographical area. This fact would be expected since these patients are advised to avoid sunlight, the main source of its synthesis. Autoantibodies against vitamin D have been described in SLE, although they do not seem to affect the vitamin circulating levels.[4] Also it was not possible to identify any difference respecting antimalarial use ratifying the findings of Fragoso et al.[20] So the use of this medication cannot be implied in the vitamin D deficiency.

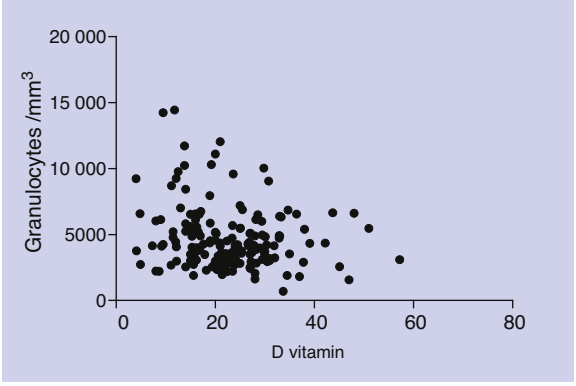

Fig. 2 – Correlation studies of serum vitamin d levels and granulocyte count (rho = −0.19;95% CI = −0.19 to −0.33; $p = 0.01$).

At present, no correlation of vitamin D levels with disease activity measured by SLEDAI was found but an interesting association of vitamin D and leukopenia was confirmed. Bogaczewicz et al.[4] have found that lower vitamin D level was linked to leukopenia in 49 SLE patients. The same finding was observed in 76 females with primary Sjögren syndrome by Baldini et al.[21] The importance of such finding is highlighted when one notes that infections are a leading cause of death in SLE patients.[22] Bacterial infections are most frequent, followed by viral and fungal infections.[22]

Vitamin D has a powerful effect in the differentiation of cells of the myeloid lineage favoring monocyte differentiation.[23] Cultures of bone marrow cells in the presence of this vitamin result in a dramatic increase of monocytes and macrophages from 12% in controls to 68% in treated cultures.[24] Furthermore, vitamin D suppresses neutrophil differentiation.[24] In a study of vitamin D-induced differentiation in cultures of normal fetal liver blast cells, a reciprocal promotion of maturation of cells from monocyte lineage and a suppression of maturation of cells restricted

to neutrophil development was observed. When treated with (OH)2 vitamin D, these cultures produced 10 times the number of monocytes than corresponding control cultures. This was reflected by the control cultures holding five times as many neutrophils as the treated cultures.[25] Ratifying these studies we found, at present, a negative association of vitamin D levels with granulocyte peripheral count. Nevertheless no association of this vitamin serum level could be found with lymphocyte count. It is important to remember that lymphocyte counts in SLE patients may be altered by others interfering factors such as the presence of lymphocytotoxic autoantibodies. These autoantibodies appear in 36–90% of lupus patients and are associated with lower count of leucocytes and with higher disease activity.[26,27] Reduced surface expression of complement regulatory proteins such as CD55 and CD59 has also been implicated in the pathogenesis of lupus lymphopenia as this deficiency will turn the cells susceptible to complement-mediated lysis.[28]

Summarizing, the present study shows that vitamin D serum levels are lower in lupus patients than in controls. No relationship of this vitamin serum level with disease activity could be found but a negative relation with leucocytes number was established. Further studies are needed in order to clarify the importance of this vitamin deficiency in the prevalence of infections in these patients.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Mathieu C, Adorini L. The coming of age of 1,25-dihydroxyvitamin D3 analogs as immunomodulatory agents. Trends Mol Med. 2002;8:174–9.
2. Conron M, Young C, Beynon HL. Calcium metabolism in sarcoidosis and its clinical implications. Rheumatology. 2000;39:707–13.
3. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. Autoimmun Rev. 2012;12:127–36.
4. Bogaczewicz J, Sysa-Jedrzejowska A, Arkuszewska C, Zabek J, Kontny E, McCauliffe DP, et al. Vitamin D status in systemic lupus erythematosus patients and its association with selected clinical and laboratory parameters. Lupus. 2012;21:477–84.
5. Birmingham DJ, Hebert LA, Song H, Noonan WT, Rovin BH, Nagaraja HN, et al. Evidence that abnormally large seasonal declines in vitamin D status may trigger SLE flare in non-African–Americans. Lupus. 2012;21:855–64.
6. Petri M, Bello KJ, Fang H, Magder LS. Vitamin D in SLE: modest association with disease activity and urine protein/creatinine ratio. Arthritis Rheum. 2013;65:1865–71.
7. Mok CC, Birmingham DJ, Leung HW, Hebert LA, Song H, Rovin BH. Vitamin D levels in Chinese patients with systemic lupus erythematosus: relationship with disease activity, vascular risk factors and atherosclerosis. Rheumatology. 2012;51:644–52.
8. Hamza RT, Awwad KS, Ali MK, Hamed AI. Reduced serum concentrations of 25-hydroxy vitamin D in Egyptian patients with systemic lupus erythematosus: relation to disease activity. Med Sci Monit. 2011;17:711–8.
9. Souto MID, Coelho A, Guo C, Mendonça LMC, Argolo S, Papi JAS, et al. Vitamin D insufficiency in Brazilian patients with SLE: prevalence, associated factors, and relationship with activity. Lupus. 2011;20:1019–26.
10. Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. Rheumatology. 2008;47:920–3.
11. Xiong J, He Z, Zeng X, Zhang Y, Hu Z. Association of vitamin D receptor gene polymorphisms with systemic lupus erythematosus: a meta-analysis. Clin Exp Rheumatol. 2014;32:174–81.
12. Emerah AA, El-Shal AS. Role of vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D level in Egyptian female patients with systemic lupus erythematosus. Mol Biol Rep. 2013;40:6151–62.
13. Mostowska A, Lianeri M, Wudarski M, Olesińska M, Jagodziński PP. Vitamin D receptor gene BsmI, FokI, ApaI and TaqI polymorphisms and the risk of systemic lupus erythematosus. Mol Biol Rep. 2013;40:803–10.
14. Silva JA, Fernandes KM, Pancotto JAT, Fragoso TS, Donadi EA, Crovella S, et al. Vitamin D receptor (VDR) gene polymorphisms and susceptibility to systemic lupus erythematosus clinical manifestation. Lupus. 2013;22:1110–7.
15. Herzinger T, Plewig G, Röcken M. Use of sunscreens to protect against ultraviolet-induced lupus erythematosus. Arthritis Rheum. 2004;50:3045–6.
16. Skare T, Ribeiro CF, Souza FH, Haendchen L, Jordão JM. Antimalarial cutaneous side effects: a study in 209 users. Cutan Ocul Toxicol. 2011;30:45–9.
17. Huisman AM, White KP, Algra A, Harth M, Vieth R, Jacobs JW, et al. Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. J Rheumatol. 2001;28:2535–9.
18. Tutuncu ZN, Kalunian KC. The definition and classification of systemic lupus erythematosus. In: Wallace D, Hahn BH, editors. Dubois' lupus erythematosus. Philadelphia: Lippincot, Willians & Wilkins; 2007. p. 16–20.
19. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, Austin A. Derivation of the Sledai: a disease activity index for lupus patients. Arthritis Rheum. 1992;35:630–40.
20. Fragoso TS, Dantas AT, Marques CD, Rocha Junior LF, Melo JH, Costa AJ, et al. 25-Hydroxyivitamin D3 levels in patients with systemic lupus erythematosus and its association with clinical parameters and laboratory tests. Rev Bras Reumatol. 2012;52:60–5.
21. Baldini C, Delle Sedie A, Luciano N, Pepe P, Ferro F, Talarico R, et al. Vitamin D in early primary Sjögren's syndrome: does it play a role in influencing disease phenotypes? Rheumatol Int. 2014;34:1159–64.
22. Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. Lupus. 2013;22:1286–94.
23. Bunce CM, Brown G, Hewison M. Vitamin D and hematopoiesis. Trends Endocrinol Metab. 1997;8:245–51.
24. McCarthy DM, San Miguel JF, Freake HC, Green PM, Zola H, Catovsky D, et al. 1,25-Dihydroxyvitamin D3 inhibits proliferation of human promyelocytic leukaemia (HL60) cells and induces monocyte-macrophage differentiation in HL60 and normal human bone marrow cells. Leuk Res. 1983;7:51–5.
25. Barton AE, Bunce CM, Stockley RA, Harrisson P, Brown G. l,25-Dihydroxyvitamin D, promotes monocytopoiesis and

suppresses granulocytopoiesis in cultures of normal human myeloid blast cclls. J Leukoc Biol. 1994;56:124–32.
26. Hepburn AL, Narat S, Mason JC. Management of peripheral blood cytopenias in systemic lupus erythematosus. Rheumatology. 2010;49:2243–54.
27. Magalhães MB, da Silva LM, Voltarelli JC, Donadi EA, Louzada-Junior P. Lymphocytotoxic antibodies in systemic lupus erythematosus are associated with disease activity irrespective of the presence of neuropsychiatric manifestations. Scand J Rheumatol. 2007;36:442–7.
28. Garcia-Valladares I, Atisha-Fregoso Y, Richaud-Patin Y, Jakez-Ocampo J, Soto-Vega E, Elías-López D, et al. Diminished expression of complement regulatory proteins (CD55 and CD59) in lymphocytes from systemic lupus eyrthematosus patients with lymphopenia. Lupus. 2006;15:600–5.