OPEN ACCESS Freely available online

Lupus: Open Access

Mini Review

Vitamin D Level and its influence on Systemic Lupus Erythematosus: an overview

Francisco José Navarro-Triviño

Unidad de Gestión Clínica de Dermatología y Venereología.

ABSTRACT

Vitamin D plays an important role as an immunomodulator and anti-inflammatory, which is why the role of vitamin D in systemic diseases has generated multiple hypotheses about its role as a possible treatment for some of them. Systemic lupus erythematosus (SLE) is a serious multisystem autoimmune diseases, which involves genetic and environmental factors. Vitamin D deficiency may play a vital role in the pathogenesis and progression of SLE. There are an inverse correlation between serum vitamin D levels and disease activity of SLE. Furthermore, low serum vitamin D levels have been correlated with, fatigue, cardiovascular diseases, anti-ds-DNA cutaneous and renal involvement, and SLE flares. Despite possible controversies between vitamin D deficiency levels and certain aspects of the SLE, what does not raise any doubt is that vitamin D supplementation with regular monitoring should be considered as part of their health management plans. Regardless of whether vitamin D deficiency in patients with SLE is cause or consequence, evaluation of vitamin D status in all SLE patients is essential and mandatory, since vitamin D deficiency has been established as a risk factor for lupus.

Keywords: Vitamin D; Systemic Lupus Erythematous; Microbiome; Cardiovascular disease; CXCL10; Lupus nephritis; SLEDAI score; Vitamin D supplementation.

INTRODUCTION

In recent years the interest of the scientific community in the role of vitamin D in multiple diseases has allowed us to understand the different functions of this vitamin. In fact, vitamin D plays an important role as an immunomodulator and anti-inflammatory, which is why the role of vitamin D in systemic diseases has generated multiple hypotheses about its role as a possible treatment for some of them. Vitamin D status varies with ethnicity and geography. Vitamin D status is determined by measuring the serum levels of 25(OH)D as this is the major circulating form of vitamin D. The majority of researchers have considered a serum level of > 30 ng/mL as sufficient. Multiple articles have been published in the literature showing the role of vitamin D in different diseases such as hydrosadenitis suppurativa, acne, vitiligo, or systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a serious multisystem autoimmune diseases, which involves genetic and environmental factors. The etiological factors are still remain unclear, while endocrine (estrogen, vitamin D deficiency, among others), genetic and environmental factors have been suggested to be potential risk factors. While the pathophysiology of SLE is incompletely understood, it is characterized by aberrant T and B cell activity, elevated autoantibody titters, and subsequent organ damage. Vitamin D deficiency may play a vital role in the pathogenesis and progression of SLE.

Vitamin D is now being increasingly recognized as a potent immunomodulator that regulates both innate and adaptive immune responses. Vitamin D has potential benefits for the treatment of patients with SLE, however, the efficacy is yet to be clarified. A high prevalence of vitamin D deficiency or insufficiency in SLE has been reported. In a study conducted in Spain, Spanish SLE patients showed than 75% of these patients presented an insufficient vitamin D levels (10-29 ng/mL) and and deficiency in 15% (<10 ng/mL). We must take into account that some of treatments mostly used in patients with SLE, such as hydroxychloroquine, corticosteroids or others

***Correspondence to:** Francisco José Navarro-Triviño, MD Unidad de Gestión Clínica de Dermatología y Venereología, Hospital Universitario San Cecilio, Granada. Avenida de la Investigación s/n, 18016. Spain. Tel: 0034657998758; E-mail: fntmed@gmail.com

Received: March 04, 2020; **Accepted:** March 13, 2019; **Published:** March 20, 2019

Citation: Navarro-Triviño FJ (2020) Vitamin D Level and its influence on Systemic Lupus Erythematosus: an overview. Lupus: Open Access 5:148. DOI: 10.35248/2684-1630.20.5.148.

immunosuppressants tend to reduce the levels of serum vitamin D. Cardiovascular diseases, cognitive function, sleep disorders and fatigue have been associated with inadequate serum levels of vitamin D in SLE. There are an inverse correlation between serum vitamin D levels and disease activity of SLE. Furthermore, low serum vitamin D levels have been correlated with, fatigue, cardiovascular diseases, anti-ds-DNA cutaneous and renal involvement, and SLE flares. It is interesting to know that certain polymorphisms such as BB genotype of VDR (Vitamin D Receptor) BsmI described by Fouad, et al [1] is associated with an increased risk of SLE among Egyptian children. Salimi, et al [2] showed that those patients with VDR rs2228570 and rs731236 polymorphisms and tAf haplotype were associated with SLE risk. On the other hand, Skp2 and p27 play vital roles in mediating the migration, proliferation and invasion of tumour cells, as well as balancing immune tolerance in the development of autoimmune diseases. Liu, et al [3] described how 1.25-(OH)2D3 reduces Skp2 protein expression, and mediated the upregulation of p27. Deficiencies of p27 induces lupus-like abnormalities. In fact, Skp2 mRNA expression in the renal tubular cells of SLE patients was significantly higher, while the mRNA expression of 1.25-(OH)2D3, VDR and p27 was significantly lower. These results indicated that 1.25-(OH)2D3/VDR downregulated Skp2 expression and upregulated p27 expression in SLE patients. The authors concluded that this finding could be a promising therapeutic target in the treatment of SLE.

The composition of the gut microbiome can be altered by vitamin D status. Vitamin D deficiency increased *Bacteriodetes* and *Proteobactaria phyla*, as demonstrated by Yamamoto, et al [4]. Low vitamin D increases the permeability of the gut barrier and heightens immune activity, furthermore can alter microbial composition and the ability to translocate microbed across the intestinal epithelium, leading to interaction with the host immune system. Changes in the microbiome possibly related to vitamin D deficiency, and it could be considered a new risk factor for the development of autoimmune diseases such as SLE.

SLE patients have an increased risk of cardiovascular disease, due mainly to an elevated burden of subclinical atherosclerosis. Ong, et al [5] published an article that related vitamin D deficiency and arterial hypertension in patients with SLE. It is possible that the effects of vitamin D on the renin-angiotensin system could justify this fact, although the mechanism has not yet been accurately described. Another of the risks associated with patients with SLE is the loss of bone mass, related both by the use of systemic corticosteroids for long periods of time, as well as the chronic pro-inflammatory state of the disease itself. Tedeschi, et al [6] showed that vitamin D supplementation did not affect change in bone turnover markers (P1NP and CTX) among SLE patients during 12-weeks with vitamin D supplementation. However, these authors concludes that it is really important to assess the need for bisphosphonates treatments to all patients with SLE that require it according to the 2017 ACR guidelines. It is essential to warn premenopausal women of the teratogenic power of bisphosphonates. In relation to the above, Sapkota, et al [7] observed the low prescription of vitamin D and/or bisphosphonates in patients diagnosed of SLE with osteoporosis according to the criteria of the 2017 ARC guidelines. In fact, the ACR recommended evaluating patients at risk of osteoporosis and associated vitamin D deficiency, and correct the vitamin D nutritional status if this were necessary. These authors concluded that safe duration of anti-resorptive therapy to improve GIOP care in SLE patients are necessary. Another association related to SLE is metabolic syndrome. Garcia-Carrasco, et al [8] described the inverse relationship between vitamin D levels, and the association with elevated triglyceride levels or metabolic syndrome. The relationship between vitamin D deficiency and the development of the metabolic syndrome is not well described, however, there is sufficient evidence from multiple studies that have linked the role of vitamin D in glucose metabolism, as well as being able to inhibit adipogenesis. In the result, patients with sufficient levels of vitamin D may act as a protective factor against the development of SLE. At the moment, this connection is still questionable. Patients with SLE associate a high risk of internal organs damage. Among them, one of the most important is the kidney. About 35% of adults with SLE show the clinical manifestation of nephritis at the time of diagnosis, and 50 to 60% of patients develop the nephritis over the first 10 years of onset of the disease. The relationship between vitamin D deficiency and the development of lupus nephritis has been studied by several authors. Among them, Abediazar, et al [9] studied the importance of a chemokine recreated by endothelial cells, fibroblasts, and monocytes, the CXCL10. The CXCL10 molecule participates in inflammatory, infectious, and autoimmune diseases, and its secretion is influenced by the presence of INF-gamma. In this study, they observed that patients with lupus nephritis showed higher levels of CXCL10 molecule and deficient levels of vitamin D. This could be related since vitamin D reduces CXCL10 secretion by macrophages, and modifies endothelial function and repairs mechanism in SLE patients, independently of SLE activity. This situation justifies the determination of vitamin D levels in patients with SLE, and correcting deficient levels since it can be considered a risk group for the development of lupus nephritis.

Recognizing the SLE as the paradigm of autoimmune diseases, and the clear involvement of the immune system in the development of the disease, it is important to know that all cells of the immune system express the vitamin D receptor (VRD) and 1 α -hydroxylase. In fact, in recent years it has been described that vitamin D has immune-modulating properties. Among them, the ability to inhibit Th1 and Th17 differentiation, while promoting Treg development stands out. In addition, vitamin D has also demonstrated inhibit B cell proliferation, and differentiation into memory B cells and antibody-secreting plasma cells. Recently Yamamoto, et al [10] has observed through an animal model study, that low levels of Vitamin D3 are associated with elevated levels of memory B lymphocytes, which could imply increase disease activity. Possibly one of the most controversial issues is the relationship between vitamin D levels and the activity of SLE disease using the SLEDAI score. This topic is mainly controversial and fuelled because of the disparate results observed in the literature. Two meta-analyses have been published regarding this topic. Zheng, et al [11] describe it as the first meta-analysis that systematically evaluated the efficacy and safety of vitamin D supplementation

in patients with SLE. These authors analyses a total of 490 patients who received vitamin D supplements ranging from 1,200 to 7,143 IU/day, for a maximum period of 12 months. As expected, vitamin D supplementation significantly increased the levels of serum 25(OH)D as compared to the placebo treatment. However, this fact did not decrease the score in SLEDAI scores. Similarly, another of the conclusions the meta-analysis is that it did not show a significant difference between the vitamin D supplementation and the placebo treatment group in titles of anti-dsDNA antibodies. However, one of the most disabling symptoms in patients with SLE is fatigue, present in up to 81% of patients with SLE. The vitamin D supplement significantly reduced the FSS score, which showed that the fatigue is improved by vitamin D supplementation, and therefore, improves the patient's quality of life. A second meta-analysis conducted and published by Guan, et al [12] described an inverse correlation between the levels of 25(OH)D and the SLEDAI score. Possibly the relationship between SLE and vitamin D deficiency is bidirectional, as described by Dutta, et al [13] Chronic proinflammatory status, and photosensitivity [14], among other factors, also appeared to be a risk factor for vitamin D deficiency. In addition, vitamin D deficiency is associated with winter flares, and high disease activity in SLE patients. Despite possible controversies between vitamin D deficiency levels and certain aspects of the SLE, what does not raise any doubt is that vitamin D supplementation with regular monitoring should be considered as part of their health management plans, as Islam, et al [15] concludes . Regarding the safety of the indication of vitamin D supplements, no severe adverse events were found. The toxicity of vitamin D mainly occurred as a result of the increased levels of serum calcium, but the authors did not observe which the vitamin D supplementation influence the serum calcium levels in patients with SLE.

CONCLUSION

In conclusion, it is clear that vitamin D plays an important role in autoimmune diseases such as SLE. Although the origin of the vitamin D deficit is unknown, it is possible that the use (or abuse) of Sunscreens, or photosensitivity, are one of the causes of it. Regardless of whether vitamin D deficiency in patients with SLE is cause or consequence, evaluation of vitamin D status in all SLE patients is essential and mandatory, since vitamin D deficiency has been established as a risk factor for lupus.

REFERENCES

1. Fouad H, Yahia S, Elsaid A, Hammad A, Wahba Y, El-Gilany AH, et al. Oxidative stress and vitamin D receptor BsmI gene polymorphism in Egyptian children with systemic lupus erythematosus: a single center study. Lupus. 2019;28(6):771-777.
2. Salimi S, Eskandari F, Rezaej M, Sandoughi M. Vitamin D Receptor rs2228570 and rs731236 Polymorphisms are Susceptible Factors for Systemic Lupus Erythematosus. Adv Biomed Res. 2019;8:48.
3. Liu D, Fang YX, Wu X, et al. 1,25-(OH)2D3/Vitamin D receptor alleviates systemic lupus erythematosus by downregulating Skp2 and upregulating p27. Cell Commun Signal. 2019;17(1):163.
4. Yamamoto EA, Jørgensen TN. Relationships Between Vitamin D, Gut Microbiome, and Systemic Autoimmunity. Front Immunol. 2020;10:3141.
5. Ong SG, Ding HJ. Vitamin D status in a monocentric cohort of systemic lupus erythematosus (SLE) patients and correlations with clinical and immunological profile. Med J Malaysia. 2019;74(6):492-498.
6. Tedeschi SK, Aranow C, Kamen DL, LeBoff M, Diamond B, Costenbader KH. Effect of vitamin D on serum markers of bone turnover in SLE in a randomised controlled trial. Lupus Sci Med. 2019;6:000352.
7. Sapkota S, Baig S, Hess T, O'Connell AM, Menk J, Shyne M, et al. Vitamin D and bisphosphonate therapy in systemic lupus erythematosus patients who receive glucocorticoids: are we offering the best care? Lupus. 2020;29(3):263-272.
8. Carrasco GM, Pinto MC, Jiménez MC, Realpozo PM, Martínez SM, Morales E, et al. 25-Hydroxyvitamin D concentrations and risk of metabolic syndrome in systemic lupus erythematosus women. Int J Rheum Dis. 2019;22(11):2067-2072.
9. Abediazar S, Nakhjavani JM, Ghorbanihaghjo A, Shekarchi M, Vahed SZ. Serum Levels of CXCL10 and Vitamin D in Patients with Lupus Nephritis. Iran J Kidney Dis. 2019;13(6): 389-397.
10. Yamamoto EA, Nguyen JK, Liu J, Keller E, Campbell N, Zhang CJ, et al. Low Levels of Vitamin D Promote Memory B Cells in Lupus. Nutrients. 2020;12(2):291.
11. Zheng R, Gonzalez A, Yue J, Wu X, Qiu M, Gui L, et al. Efficacy and Safety of Vitamin D Supplementation in Patients With Systemic Lupus Erythematosus: A Meta-analysis of Randomized Controlled Trials. Am J Med Sci. 2019;358(2):104-114.
12. Guan SY, Cai HY, Wang P, Lv TT, Liu LN, Mao YM, et al. Association between circulating 25-hydroxyvitamin D and systemic lupus erythematosus: A systematic review and meta-analysis. Int J Rheum Dis. 2019;22(10):1803-1813.
13. Dutta C, Kakati S, Barman B, Bora K. Vitamin D status and its relationship with systemic lupus erythematosus as a determinant and outcome of disease activity. Horm Mol Biol Clin Investig. 2019;38(3).
14. Irastorza RG, Egurbide MV, Olivares N, Berriotxoa MA, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. Rheumatology (Oxford). 2008;47(6):920-923.
15. Islam MA, Khandker SS, Alam SS Kotyla P, Hassan R. Vitamin D status in patients with systemic lupus erythematosus (SLE): A systematic review and meta-analysis. Autoimmun Rev. 2019;18:102392.