



Review Article

Bone Health, Vitamin D and Lupus[☆]

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ABSTRACT

The prevalence of vitamin D deficiency and insufficiency among patients with systemic lupus erythematosus is high. This is likely due to photoprotection measures in addition to intrinsic factors of the disease. Low levels of vitamin D increase the risk of low bone mineral density and fracture. Vitamin D deficiency could also have undesirable effects on patients' immune response, enhancing mechanisms of loss of tolerance and autoimmunity. Vitamin D levels should be periodically monitored and patients should be treated with the objective of reaching vitamin D levels higher than 30–40 ng/ml.

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Salud ósea, vitamina D y lupus

RESUMEN

Los pacientes con lupus eritematoso sistémico presentan una prevalencia elevada de deficiencia e insuficiencia de vitamina D. Esto se debe probablemente a las medidas de fotoprotección y a factores intrínsecos de la enfermedad. Los niveles bajos de vitamina D aumentan el riesgo de presentar una densidad mineral ósea reducida y de fractura. El déficit de vitamina D podría también tener efectos no deseados sobre la respuesta inmune de los pacientes, potenciando mecanismos de pérdida de tolerancia y autoinmunidad. Los niveles de vitamina D deberían ser monitorizados periódicamente y los pacientes deberían ser tratados con el objetivo de alcanzar unos niveles de vitamina D superiores a 30–40 ng/ml.

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Palabras clave:

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that primarily affects women of childbearing age. Significant advances in treatment, achieving a more efficient control of inflammatory disease activity, have led to a progressive increase in the life expectancy of patients. Unfortunately, most of them gradually accumulate irreversible damage during the course of the disease, which compromises their quality of life and reduces life expectancy, the latter at the expense primarily of accelerated atherosclerosis. The development of osteoporosis and the appearance of associated fractures are very important components of irreversible damage, accrued in the medium and long term, and hypovitaminosis D¹ may be involved in its development.

Vitamin D is a steroid hormone that plays a crucial role in mineral metabolism and bone homeostasis, interacting with the parathyroid gland, kidney and gut. Although historically it has been classified as an essential diet-obtained vitamin, vitamin D can be synthesized in humans and most mammals endogenously, its main source being the conversion of 7-dehydrocholesterol to provitamin D₃ in the skin through ultraviolet B radiation from the sun. Through exposure to ultraviolet light, provitamin D₃ becomes previtamin D₃, which is isomerized to vitamin D₂ and transported to the bloodstream. In the liver, 25-hydroxylase converts vitamin D₂ quickly into 25 (OH) D₂ and 25 (OH) D₃ (calcidiol), considered as storage forms of vitamin D. Both the 25 (OH) D₂ and 25 (OH) D₃ forms are released into the blood. In renal tubular cells, 1- α -hydroxylase converts 25 (OH) D₃ into 1,25 (OH)₂ D₃ or calcitriol, which is the biologically active compound, increasing intestinal absorption of calcium and phosphate, increasing bone mineralization and stimulating osteoclast differentiation. Activity of 1- α -hydroxylase is stimulated by PTH and hypocalcemia and is suppressed by serum calcitriol and phosphate. The presence of 1- α -hydroxylase in various tissues and in different cells of the immune system has been

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recently described, making possible, at least in theory, *in situ* production of calcitriol, with potential autocrine or paracrine effects.²

Numerous studies in different regions of the world have shown that vitamin D insufficiency is a very common problem at all ages and results from the combination of a number of factors such as race, degree of sun exposure, latitude, aging and intake of vitamin D.³ In addition to the role of vitamin D deficiency in the development or severity of osteoporosis, information on the potential link between vitamin D deficiency and various autoimmune diseases, hypertension and some cancers³ is accumulating. In recent years, the discovery of the vitamin D receptor (VDR) in immune cells as well as the fact that many of these cells endogenously produce calcitriol suggest that it may have four immunoregulatory properties. The inhibitory properties on cell proliferation, enhancement of cell differentiation, anti-inflammatory and immunomodulation roles of synthetic VDR agonists could be used to treat a variety of autoimmune diseases such as rheumatoid arthritis, SLE, multiple sclerosis and inflammatory bowel disease.⁵ Moreover, vitamin D deficiency could divert the immune response to a loss of tolerance⁴ making the treatment of vitamin D deficiency particularly important in patients with lupus. In fact, a direct relationship between lupus activity and states of hypovitaminosis D has been proposed.⁶

The objective of this narrative review is to analyze and integrate the latest relevant information on the implications of vitamin D deficiency in patients with SLE, both regarding bone health as well as the implications on autoimmunity and atherosclerosis.

Vitamin D Deficiency and Lupus

Calcidiol concentration in serum is the most accepted indicator of the reserve of vitamin D in the body. However, this determination is not standardized and there is no general consensus regarding what serum reference values are. Although vitamin D insufficiency was initially defined as a mild form of vitamin D deficiency that leads to hyperparathyroidism and decreased bone mass without osteomalacia or hypocalcemia, currently vitamin D insufficiency has been redefined as a concentration below 70 nmol/L (30 ng/ml) without reference to the levels of PTH in July.⁷ Although there is controversy regarding the optimal level of vitamin D, current information from observational and biochemical studies and randomized clinical trials indicates that serum levels of at least 50 nmol/L are required to normalize PTH, minimize the risk of osteomalacia and ensure optimal cell function.⁸

There is a relationship between vitamin D deficiency and various autoimmune diseases. In fact, populations farthest from the equator are at increased risk of developing autoimmune diseases.⁹ We have solid evidence on the association between SLE or rheumatoid arthritis and vitamin D deficiency, although there is also probably an association with other chronic inflammatory rheumatic diseases.¹⁰ Studies in groups of patients with autoimmune rheumatic diseases have shown a high prevalence of low levels of vitamin D. Thus, 1029 patients with various autoimmune diseases such as scleroderma, polymyositis, dermatomyositis, antiphospholipid syndrome, rheumatoid arthritis or SLE had lower levels of calcidiol than healthy controls.¹¹ However, one must take into account the heterogeneity of the cutoff points used in different studies and possible confounding factors associated with various diseases, such as glucocorticoid treatment, photosensitivity or recommendations to avoid sun exposure.

Patients with lupus often exhibit photosensitivity, implying a higher risk of developing vitamin D deficiency. Multiple studies investigating the possible association between the insufficiency or deficiency of vitamin D and lupus have shown that vitamin D insufficiency is a very common problem in this group of patients, with a wide range of prevalence, from 16% to 96%.^{12–20} There are

many factors potentially involved in the development of hypovitaminosis D, among which we find the advice to avoid sun exposure in patients with photosensitivity; the use of sun protection measures; renal failure; prolonged use of corticosteroids, antimalarials or antiepileptic drugs; or the presence of antibodies antivitamin D.

As far back as in 1979 Canadian researchers determined calcitriol levels in 12 adolescents with SLE and found reduced levels in 7 patients. However, levels of calcidiol, which is the best marker of vitamin D available²¹ was not informed.

In a cross-sectional study in 25 patients with SLE and 25 Caucasian women with fibromyalgia there were no significant differences between the 2 groups regarding calcidiol, calcitriol and PTH determinations, with half of the patients showing vitamin D deficiency.²²

In a Danish case-control study, calcidiol and calcitriol levels were measured in 21 patients with SLE, 29 patients with rheumatoid arthritis, 12 patients with osteoarthritis and 72 healthy controls; researchers found significantly lower calcidiol levels in lupus patients than in osteoarthritis patients or healthy controls while calcitriol levels between groups did not differ significantly.²³

In a cohort study of 123 patients with newly diagnosed SLE and 240 controls, a trend towards lower levels of vitamin D was detected in SLE patients compared with controls, with a significant difference between white subjects with the control group, after adjusting for age, sex, season and smoking. Overall, 67% of subjects had vitamin D deficiency, with a reduced mean concentration among black subjects (1 5.9 ng/ml) compared with Caucasians (31.3 ng/ml). In 22 patients, critically low levels were observed, below 10 ng/ml, the most powerful predictor of renal involvement (OR 13.3; $P < .01$) followed by photosensitivity (OR 12.9; $P < .01$).⁶

In our Mediterranean environment, Muñoz Ortego et al.,²⁴ reported a prospective cohort of 73 patients with SLE who were not receiving vitamin D, in which 68.5% had vitamin D levels below 30 ng/mL. Predictors found were daily use of sunscreen and a high rate of bone mass. Instead, they showed no association between low levels of vitamin D and lupus activity or accumulated damage.²⁴

In another Spanish cohort of 92 patients (90% female and 98% white) with lupus, Ruiz Irastorza et al.,¹² found a prevalence of deficiency and insufficiency of vitamin D of 15 and 75%, respectively. Predictors of adequate levels of vitamin D were treatment with vitamin D and calcium ($P = .049$), female gender ($P = .001$) and treatment with hydroxychloroquine ($P = .014$). Photosensitivity and photoprotection were significantly associated with vitamin D insufficiency and deficiency, respectively. Vitamin D deficiency was associated with greater fatigue but vitamin D levels were not associated with the severity of SLE or duration of the disease.

Bone Health and Lupus

The causes of bone loss in SLE include traditional risk factors of osteoporosis as well as side effects on bone because of long-term use of corticosteroids and immunosuppressive drugs. However, the disease itself may condition a reduced bone mass through mechanisms such as decreased mobility, deterioration of renal function, associated endocrine dysfunction or systemic proinflammatory stimulatory cytokine effect on bone resorption.^{25,26} Recognizing the major contributing factors for bone loss in these patients could allow the early detection of osteoporosis and optimize bone health of patients, minimizing the risk of fracture.

Lupus patients exhibit decreased bone mineral density (BMD) and increased risk of fracture.²⁵ By some estimates, the frequency of osteopenia and osteoporosis could range up to 50% and 23%, respectively.^{26,27} Despite some inconsistent data between different cross-sectional studies, most of the available information supports

the association between low BMD and lupus, even in young fertile women.

Teichman et al.²⁸ studied lumbar spine and hip BMD in a group of 20 premenopausal women diagnosed with lupus of less than a year. Comparing this data with healthy controls of the same age, women newly diagnosed with SLE had significantly lower lumbar spine BMD but no significant differences were observed on the femoral neck.

In a study conducted by Norwegian researchers²⁹ BMD similarly decreased at the lumbar spine, femoral neck and total hip when comparing 75 lupus patients with 75 patients with rheumatoid arthritis, even when stratifying for menopausal status. All patients in the study were white and mostly women. No significant differences in body mass index, use of disease-modifying drugs or cytotoxic agents in patients with low BMD were observed.

Kipen et al.³⁰ assessed changes in BMD in 32 premenopausal women with SLE, with a mean age of 35 years, showing only minimal changes in lumbar spine and femoral neck BMD. Physical activity was a protective factor against BMD loss of the femoral neck.

In a similar study, Jardinet et al.,³¹ observed a significant decrease in lumbar spine BMD from baseline from 1.22% per year in 35 women of childbearing age with SLE and a mean age of 30 years, after a mean follow-up of 21 months. However, they found no difference in the change in hip BMD. The patients had a significantly lower baseline BMD than age-matched healthy controls.

Jacobs et al.,³² recently published a longitudinal study with the largest number of patients enrolled till date: 126 patients with SLE, 90% female, mean age 39 years. At baseline, 39.7% of patients had osteopenia and 6.3% osteoporosis. After a mean follow-up of 6 years, changes in lumbar spine (−0.08%/year) and hip BMD (−0.20%/year) were not significant compared to baseline. During follow-up, 70% of patients were treated with glucocorticoids. The multiple regression analysis showed that the decrease in lumbar spine BMD was significantly associated with glucocorticoid dose and reduced levels of vitamin D. The loss of bone mass in the hip was associated with lower levels of the vitamin, to a lower body mass index and the use of antimalarials at the start of follow-up.

There are few studies evaluating fracture risk in patients with SLE. In a population of 702 women (mean age 33.2 years) with SLE followed for an average of 8 years, Ramsey-Goldman et al.,³³ showed that 12.3% of women had at least one fracture non-attributable to severe trauma after the diagnosis of SLE.

Vitamin D, Immune Response and Clinical Activity in Lupus

Despite the numerous studies published on LES and vitamin D, a question to be answered is whether vitamin D deficiency aggravates the course of disease. This is the point most recent published studies have focused on, reflecting some inconsistency in the findings. These conflicting results could be explained by the diversity of the study populations, methodological variations or that some studies are underpowered due to the number of patients included.³⁴

The discovery of the VDR on most cells of the immune system suggests a number of immunomodulating actions related to vitamin D. *In vitro* studies have shown that calcitriol modulates both innate and adaptive immune responses. Vitamin D increases the chemotaxis and phagocytosis of macrophages and increases the production of IL-12 and IL-13, leading to a change of polarization of T cells by altering their phenotype Th1 and Th17 to Th2. Calcitriol also inhibits B cell differentiation to plasma cells and immunoglobulin production of IgM and IgG isotypes.³⁵ In SLE, many of the immunomodulatory actions of vitamin D are opposite to those observed with disease activity, so one hypothesis states that vita-

min D deficiency could be considered a risk factor for development that arises or perpetuation of activity in SLE. However, this attractive hypothesis could not be confirmed in a study conducted in a cohort of more than 180,000 US nurses.³⁶

Petri et al.,³⁷ studied the association between vitamin D levels and different parameters of activity in a prospective cohort of 1006 patients with SLE (91% female, 54% white) that were followed for a mean of 128 weeks. Patients with lower levels of calcidiol 40 ng/ml were supplemented with 50,000 units of vitamin D2 weekly. An increase of 20 units in calcidiol levels was associated with a decrease in the rate of SELENA-SLEDAI activity of 0.22 points, which corresponded with a 21% decrease in the *odds ratio* of presenting a higher SLEDAI SELENA-4. Moreover, the mean protein/creatinine ratio decreased by 2% ($P=.0009$), which corresponded with a 15% decrease in the *odds ratio* of presenting a protein/creatinine ratio greater than 0.5.

Borba et al.,¹⁹ found no association between lupus activity, measured by the SLEDAI-2 K index, and the levels of IL-6, IL-1 and TNF α and with low levels of vitamin D in 36 patients with SLE. Furthermore, the multiple regression analysis showed that reduced levels of calcidiol were associated to elevated levels of osteocalcin and bone alkaline phosphatase.

In another study, Amital et al.¹³ determined calcidiol levels in 378 patients with SLE and related to the SLEDAI-2 K activity indices in 278 patients and ECLAM in 100 patients. They concluded that there was a significant negative correlation between serum vitamin D levels and standardized disease activity since, although the association was weak, statistical significance was reached.

Mok et al.,³⁸ studied the sensitivity and specificity of vitamin D deficiency as a predictor of systemic lupus activity and damage compared with classical markers of activity, such as the concentration of anti-native DNA and anti-C1q antibodies in a cohort of 290 patients with SLE, 95% female, with a mean age of 39 years and a mean disease duration of 7.7 years. They concluded that vitamin D deficiency was a marker of SLE activity, with comparable levels of anti-C1q antibody specificity. However, they found no significant association between calcidiol deficiency and accumulated systemic organ damage.

Thudi et al. reported that³⁹ 20% of SLE patients had calcidiol levels of less than 47.7 nmol/l. These patients had a significantly higher mean disease activity, including overall evaluation indices, than patients with normal levels of vitamin D.

Recently, Sakthiswary and Raymond³⁴ have published a systematic review of the clinical significance of vitamin D in lupus. They identified eight case-control studies and 14 cohort studies. Of the 15 studies linking vitamin D and SLE activity, 10 showed an inverse relationship between vitamin D levels and lupus activity. In relation to the accumulated disease damage, 5 of 6 studies investigating the association found no significant difference. The authors concluded that there was sufficient evidence on the association between the states of vitamin D deficiency and SLE disease activity but not with indices of cumulative damage.

Vitamin D and Cardiovascular Risk in Lupus

Vitamin D deficiency has been linked to coronary artery disease, heart failure and kidney disease.^{40–42} Ischemic heart disease is a leading cause of death in patients with SLE, so it is very important to identify factors associated with the development of atherosclerosis in lupus patients.

Mok et al.,³⁸ in their sample of 290 patients, showed that subjects with vitamin D deficiency (<15 ng/ml) had a significantly higher ratio LDL cholesterol/total cholesterol. These findings are consistent with those of Wu et al.,¹⁸ who showed a correlation between high levels of LDL-cholesterol and low levels of vitamin

D. Reynolds et al.,⁴³ and Ravenell et al.,⁴⁴ have published contradictory results on the correlation with carotid atheroma plaque. Ravenell et al. showed that vitamin D levels correlated inversely with the total area of plaque when age-adjusted, while Reynolds et al. could not demonstrate this association, although a significant increase in aortic stiffness was associated with low levels of vitamin D.

In a study of Kiani et al.,⁴⁵ no significant association between vitamin D levels and any measure of subclinical atherosclerosis and coronary calcification quantified by CT, or thickness of carotid intima-media measured by ultrasound was found in 154 patients with SLE.

Supplementation With Vitamin D in Lupus

30–40 ng/ml are considered the minimum desirable calcidiol serum levels since lower concentrations lead to different degrees of hyperparathyroidism. To standardize the concentration of vitamin D, doses of about 10 000 U daily vitamin D2 are required and 3 months of treatment.³ Calcium supplements and vitamin D are clearly indicated in some situations such as rickets or in the context of the use of drugs for osteoporosis. However, in other clinical situations there may be doubts on the advisability of supplementation.⁴⁶ A meta-analysis of 18 studies with randomized controlled trials showed that patients receiving vitamin D had a reduction in mortality versus⁴⁷ patients in the placebo group.

From the immunological point of view, it has been observed that vitamin D deficiency diverts the immune response to a loss of tolerance. The addition of vitamin D reversed immunological abnormalities characteristic of SLE⁴⁸ and supplementation induces beneficial clinical and immunological effects in experimental models of SLE.⁴⁹ Some authors advocate treatment with vitamin D as prevention of autoimmune disease perpetuation. In this respect Abou-Raya et al.,⁴⁸ carried out a randomized, double-blind, placebo-controlled trial with a population of 267 SLE patients (228 women, 39 men, mean age 38.8 years, mean disease duration 8.2 years) and determined vitamin D homeostasis and inflammatory markers and parameters of disease activity before and after administration of vitamin D. The average baseline calcidiol was 19.8 ng/ml in patients compared with 28.7 ng/ml in controls. The overall prevalence of baseline suboptimal levels and calcidiol deficiency in SLE patients and controls was 69 and 39%, respectively. The suboptimal vitamin D levels were significantly correlated with lupus activity. At 12 months of treatment, a significant improvement in the levels of inflammation and homeostasis, as well as disease activity in the treatment group compared to the placebo, was seen.

Conclusions

Vitamin D is essential for many body tissues and is involved in numerous biological processes beyond bone metabolism. There is sufficient epidemiological evidence that shows that low levels of vitamin D are associated with various medical conditions, particularly with autoimmune diseases. The demonstration of a higher prevalence of vitamin D deficiency in SLE patients compared with healthy controls, coupled with the recent discovery of its immunomodulating properties in both innate and adaptive responses, has attracted interest in this field with the objective of demonstrating a clinical role of vitamin D in the course of SLE. SLE patients have a higher prevalence of osteopenia and osteoporosis, even in young premenopausal women, as a result of various factors, among which the use of glucocorticoids, vitamin D deficiency and the activity of the disease are included. It is essential to identify these factors early to reduce the risk of fracture. Although

recent data suggest the existence of an association between states of vitamin D deficiency and SLE activity, there is still neither enough evidence to affirm categorically that an association exists nor has the impact of substitution treatment with vitamin D on the activity of the disease been fully understood. Therefore, prospective randomized controlled therapeutic intervention studies are needed.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of Interest

The authors have no conflict of interest to state.

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