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Bone mineral density and vitamin D status in systemic lupus erythematosus (SLE): a systematic review

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Conflict of interest

Tarek Carlos Salman-Monte, Vicenç Torrente-Segarra, Ana Leticia Vega Vidal, Patricia Corzo and Jordi Carbonell-Abelló declare that they have no conflict of interest.

Abstract

Despite the improvement in the quality of life of patients with SLE due to scientific and technological advances, SLE remains a disease that over the years may produce irreversible damage to patients. Osteoporosis and secondary bone fractures are two of the major causes of irreparable injury in patients with SLE. Vitamin D insufficiency may play a vital role both in reduced Bone Mineral Density (BMD) and in the appearance of fractures, although its mechanisms of action are still unclear. We performed a systematic review of the literature in order to determine the prevalence and predictors of reduced vitamin D plasma levels, bone loss and the presence of fractures in SLE patients. Our review encompassed all English-language publications using Medline and EMBase electronic databases from their inception (1966 and 1980, respectively) to December 2016. We included all intervention studies and observational studies in which vitamin D plasma levels, BMD and bone loss were measured and applied to patients with SLE. Previous studies suggested an increase in bone loss and fracture in patients with SLE compared with general population and although there is a high prevalence of vitamin D insufficiency in the general population, previous studies had demonstrated lower vitamin D levels in patients with SLE compared to age-matched controls. The etiology of reduced bone mass and reduced vitamin D plasma levels in SLE is multifactorial and includes a variety of intrinsic factors related to the disease itself and treatment side effects. SLE patients are at risk for developing these two comorbidities (reduced vitamin D plasma levels and low BMD) and it is therefore essential to study, monitor, prevent and treat bone metabolism disorders in SLE patients.

Introduction

Management of SLE, a systemic autoimmune disease with a wide range of clinical expressions, is often complicated. Despite recent scientific and technological advances and improved patient survival, SLE is still a dangerous disease that can cause irreversible damage to patients (1). Osteoporosis and secondary bone fractures are two important causes of irreparable injury in patients with SLE. Vitamin D insufficiency may play a vital role both in reduced Bone Mineral Density (BMD) and in the appearance of fractures, although its mechanisms of action are still unclear (2). The exact degree to which inflammatory activity per se, versus vitamin D plasma levels or BMD, contributes to the presence of fractures remains an open question. Preventing these two comorbidities, insufficient vitamin D levels and reduced BMD, can facilitate clinical improvement in patients with SLE, a condition in which the preservation of numerous factors related to quality of life is of the utmost importance (3).

The immunomodulatory role of vitamin D have been described in the context of autoimmunity and multiple studies have demonstrated a high prevalence of vitamin D deficiency in other autoimmune diseases as rheumatoid arthritis (4), systemic sclerosis (5) and sjögren syndrome (6).

Osteoporosis is a condition of decreased bone mass density that increases the bone fracture risk. The continual resorption and re-deposition of bone mineral, or bone remodeling, are intimately tied to the pathophysiology of osteoporosis. Previous studies have suggested an increase in bone loss and fracture in patients with SLE compared with general population (7). Moreover, although there is a high prevalence of vitamin D insufficiency in the general population, previous studies have demonstrated lower vitamin D level in patients with SLE than age-matched controls (8,9). The origin of these two conditions is multifactorial and the objective of this systematic literature

review is to describe the prevalence and predictors of these two comorbidities vis-à-vis the natural history of this disease.

Methodology

We conducted a systematic review of all English language publications using Medline and EMBase electronic databases from their inception (1966 and 1980, respectively) to December 2016. We included all intervention studies and observational studies in which vitamin D plasma levels, BMD and bone loss were measured and applied to patients with SLE. In addition, clinical experts were contacted and bibliographies of existing publications were reviewed. MeSH terms (medical subject headings) included vitamin D plasma levels, bone mineral density (BMD), bone loss, fracture risk and systemic lupus erythematosus (SLE). Data abstraction was conducted by 5 investigators (TCSM, VTS, ALVV, PC and JCA).

Bone loss in SLE

Previous studies have suggested possible bone loss and fracture risk in patients with SLE (3,10). Reduced bone mass in SLE male (11) and female (12) patients has been shown to be more prevalent compared to age-matched healthy controls. Osteoporosis is defined as a systemic skeletal disease characterized by decreased bone mineral density (BMD) (13) and an increase in the susceptibility to bone fractures. Traditionally, osteoporotic fractures are localized in several specific skeletal sites: hip, wrist and spine. There is recent evidence that autoimmunity and associated inflammation and even vitamin D deficiency play key roles in the pathogenesis of negative skeletal effects in SLE patients (2). Several factors such as physical inactivity, persistent

inflammation, and corticosteroids treatment may contribute to the presence of decreased bone mass in SLE. Osteopenia in the lumbar spine and or the hip has been reported in 25–74% of patients with SLE, and osteoporosis in 1.4–68% of patients with SLE in cohort studies (14). This wide variation might be due to differences in body mass index (BMI), age, sex, ethnic background, disease severity, medication use and study design.

The etiology of reduced bone mass in SLE is multifactorial and includes a variety of intrinsic factors related to the disease itself and to treatment side effects. Previous studies have demonstrated that postmenopausal status, older age, longer SLE disease duration, low body mass index, organ damage, impaired renal function, markers of inflammation, low 25-hydroxyvitamin D (25(OH) D) serum levels, and higher number of deliveries are risk factors for low BMD (15). Regardless of the SLE therapy chosen, some studies with SLE patients had shown corticosteroid-induced bone loss (15), while others found no differences (16,17). Disease damage and disease severity have been associated with bone loss in SLE populations (17,18). Most of the studies showed that SLE patients had lower BMD at the lumbar spine (mostly trabecular bone) (19) than at the hip (mixed bone) (18). Nevertheless, a systematic literature review and subsequent meta-analysis were published (20). Of the initial 1246 articles, only 21 articles that assessed the prevalence of reduced BMD in SLE and the presence of fracture and associated factors were selected. Twelve of these 21 articles showed that patients with SLE had significantly lower levels of BMD in the femoral neck than controls (WMD = -0.06 g / cm² CI 95% CI -0.07 to -0.04; p <0.001), which indicates that patients with SLE had an absolute decrease of 0.06 g / cm² in the mean level of BMD at the femoral neck, compared with controls. Similar findings were recorded in the lupus patient cohort from the outpatient Lupus Unit at Parc de Salut Mar-IMAS in 2015, in which femoral the neck was the region with the lowest BMD. In addition, a significant relationship between low BMI and low BMD was similarly found in the regions of total

hip and femoral neck in this patient cohort (2). These findings demonstrate the necessity of evaluating BMD not only at the spine but also at the femoral neck and hip in patients with SLE.

As mentioned, the exact degree to which inflammatory activity *per se*, versus vitamin D plasma levels and BMD, contributes to fractures remains as an open question. An interesting and recently published study involving markers of bone turnover assessed bone metabolism in 60 male Chinese patients recently diagnosed with SLE. Here, osteocalcin (bone formation marker) was negatively associated with SLE disease activity, while β -crosslaps (bone resorption marker) was positively associated with SLE disease activity. This suggests that SLE disease activity itself directly contributed to the development of SLE-associated low BMD (21).

In regards to corticosteroids treatment, although its effect on RANK-L (22) is well known, the true incidence of low BMD in SLE patients taking corticosteroids remains an open question. In the Dutch cohort of SLE patients published in 2013 (15), in which BMD and the factors that could influence it were followed for up to 6 years, an association was found between reduced BMD and corticosteroids use. For all these reasons, and despite several studies that found no such association (16), we believe there is sufficient evidence to recommend vigilance in detecting and preventing osteoporosis in patients with SLE and extended use of corticosteroids. In fact, apart from the direct action on bone tissue by corticosteroids, the presence of low vitamin D levels may generate a secondary hyperparathyroidism, which is another mechanism that accentuates bone resorption.

To date, many retrospective and transversal studies have examined the predictive factors of bone loss in SLE. In contrast, there have been few longitudinal studies (15,

23, 24, 25, 26, 27) evaluating BMD variations and associated factors. Following our own systematic literature review, we believe that the best way assess BMD in patients with SLE should be a prospective longitudinal study. This is because it would not only more clearly identify valuable predictive factors of bone loss, but also better detect various confounding factors than transversal studies might wrongly implicate. One example of this is the current controversy surrounding the use of corticosteroids, as some cross-sectional studies found no association between corticosteroids use and decreased BMD (16). However, all of the reviewed longitudinal studies (15, 23, 24, 25, 26, 27) did note a positive correlation between corticosteroids use and reduced BMD.

These observations are particularly important for patients with SLE since the causes of increased bone fragility in patients with SLE remain unclear.

In conclusion, this systematic review provides strong evidence on the relationship between SLE and bone loss and fracture risk. Not only do SLE patients have significantly lower BMD than controls, but SLE is also associated with increased fracture risk. Clinicians should be aware of these findings, which underscore the importance of preventing bone loss and the need for detecting and treating osteopenia and osteoporosis in patients with SLE. Nonetheless, many questions remain open and further studies are needed to clarify these questions.

Vitamin D and systemic lupus erythematosus

Vitamin D is a hormone involved in the regulation of calcium homeostasis, which allows calcium absorption in the gastrointestinal system. This homeostasis is maintained by the interaction of vitamin D with parathyroid hormone, kidney and intestinal tissues (28). It is synthesized in the skin via ultraviolet radiation or can be taken orally. Apart

from the classic factors for vitamin D deficiency in the general population, there are others related to SLE itself, including the use of corticosteroids, photosensitivity and SLE activity, among others, which make the study of this hormone so interesting in a disease like SLE. There are some additional renal actions involving vitamin D and its role not only in maintaining calcium homeostasis, but also in immune system functionality is well known (29).

There is a high prevalence of vitamin D deficiency in the general population, although age-matched case-control studies have shown lower levels of vitamin D in SLE patients than in healthy controls (8,30).

Several recent publications have described various immunological actions of 1,25 (OH) 2D: among others, it inhibits Th1 immune response, stops the maturation of different proinflammatory cytokines such as IFN alpha by dendritic cells and preservation of the innate response, (31,32), and acts as an immune modulator in different autoimmune diseases such as SLE (33). It is also well known that the vitamin D receptor (VDR) is expressed in almost all cells of the immune system (31).

Vitamin D insufficiency [defined as a plasma level of 25 (OH) D $\leq$ 30 ng / ml] is highly prevalent among patients with SLE, even in the southern regions (34,35). In the population-based Carolina Lupus Inception Cohort Study, 67% of the subjects were vitamin D deficient (36). These results were very similar to previous cross-sectional studies in which 68.5 % of the patients exhibited vitamin D insufficiency (35).

To date, the factors that have been associated with lower levels of vitamin D in patients with SLE are: daily sunscreen use (35), high BMI (36), lack of sun exposure and absence of treatment with hydroxychloroquine (37) (as it is known that hydroxychloroquine increases levels of 25 (OH) at the expense of reduced levels of the

active metabolite 1,25 (OH) 2D), the use of glucocorticoids, seasonal changes, serum creatinine (38), nephritis (39), altered protein / creatinine ratio (40) , low bone mineral density and fragility fractures (41), and shorter length of telomeres in African-American patients with SLE (42).

Recently, the presence of low levels of vitamin D has been associated with a higher prevalence of cardiovascular risk factors such as hypertension and hyperlipidemia (43), as well as sleeping disorders (44) and fatigue (45). Many (33,46-53), but not all, (34, 35, 45, 54-57) studies of 25(OH) D in patients with SLE have shown an association between 25(OH) D deficiency and increased SLE activity. It is important to note that 4 out of the 7 studies that did not find the latter association were performed in Spanish populations (32, 42, 51, 54). Therefore, sociodemographic and ethnic factors could influence this type of association.

As mentioned, the presence of low levels of vitamin D has recently been associated with fatigue and sleeping disorders. Fatigue is a subjective parameter difficult to quantify, but present in up to 90% of patients with SLE, with a consequent impact on their quality of life (58). Fatigue has also been linked with low vitamin D levels in Iranian nurses (59) and these same findings have been described in another Spanish series of SLE patients (45,57), thus revealing the potential role of vitamin D in the pathophysiology of fatigue. It is unknown whether insufficient vitamin D influences the level of fatigue in patients with SLE or vice versa, if patients with SLE and fatigue have inadequate levels of vitamin D. Recently, in a clinical trial of patients with juvenile SLE, investigators observed improved fatigue-scale scores after a period of 6 months with vitamin D supplementation (60).

It is known that glucocorticoids activate the destruction of 25 (OH) D and 1,25 (OH) 2 D into inactive calcitriol acid. In 2010, Toloza et al. identified seasonal changes, as well

as cumulative doses of glucocorticoids and serum creatinine, as factors associated with reduced levels of 25 (OH) D (38). In turn, they have now linked insufficient plasma levels of 25 (OH) D with daily doses of corticosteroids in Thai SLE patients (61). Recently, a correlation between insufficient vitamin D plasmatic levels has been described in a study that also examined the use of oral corticosteroids in female SLE patients (57). In fact, there was a positive correlation between the use of oral corticosteroids and vitamin D insufficiency among patients without vitamin D supplementation (versus overall patients), though this was not observed in the group of supplemented SLE female patients (58). Interestingly, in the last European Meeting of Rheumatology (EULAR), Lomarat W et al. (62) presented a study which found that high doses of ergocalciferol could serve as a safe adjunctive therapy, one that generated a corticosteroid-sparing effect, on patients with SLE.

Vitamin D insufficiency has been previously associated with reduced bone mineral density (BMD) and fractures in SLE patients, as well as in the general population (15, 63, 64). Although vitamin D has even been described as a protective factor against fracture, the exact underlying mechanisms remain unclear. Prior to this, the outpatient Lupus Unit at Parc de Salut Mar-IMAS similarly found no association between reduced BMD and patients with vitamin D insufficiency (2).

Why vitamin D plasma levels in lupus patients do not increase despite good dietary or pharmacological supplementation might be due to possible malabsorption of vitamin D supplements by an SLE-specific gastrointestinal problem. To date, however, the only things documented are that the malabsorption in SLE, which has a prevalence of 9.5%, is sometimes associated with celiac disease, and that patients with the latter have a 3X higher risk of developing SLE compared to general population (65,66).

Based on our systematic review of the literature we believe that as numerous factors can influence plasma levels of 25 (OH) vitamin D, studies seeking to evaluate predictor factors of vitamin D insufficiency in SLE patients should be carried out using a specific randomized clinical trial or case and control studies. Clear examples of the latter are the studies of Lima et al. (60) and Lomorat W et al. (62), both of which provided important recommendations for improving fatigue scores and preserving oral corticosteroids with vitamin D supplementation. We believe that studies of similar design could provide more reliable and relevant conclusions to the scientific community regarding predictors of vitamin D insufficiency in patients with SLE. The authors have realized that the doses employed in clinical trials during recent years are on the rise to abnormally high levels for achieving significant results in clinical parameters in SLE patients under vitamin D supplementation.

In conclusion, this systematic review provides published evidence on the relationship between vitamin D status and SLE patients. These patients have significantly lower 25 (OH) vitamin D than healthy people. Clinicians should be aware of these findings, which underscore the importance of preventing low vitamin D plasma levels in patients with SLE, based not only on the impact of calcium metabolism, but also other potential effects, such as fatigue symptoms, reduction of SLE activity and corticosteroids-sparing effects. Many questions remain unanswered, and further studies are needed to clarify these issues.

Conclusions

The expression of these two situations (reduced vitamin D plasma levels and low BMD), illustrates how preventable comorbidities can increase SLE disease activity, resulting in accumulated damage, worse prognoses, and the need for other therapies

in SLE patients. In these patients, musculoskeletal problems are the most prevalent symptom while pain levels can become increasingly incapacitating when an osteoporotic fracture occurs. As previously stated, choosing an appropriate design for evaluate these variables (BMD, bone loss and vitamin D plasma levels) is imperative in SLE patients, not only to avoid confounding factors, but also to permit accurate defining of the real predictors affect such aforementioned variables. It has been postulated that good control of disease activity and monitoring of BMD and vitamin D plasma levels are useful tools for improving bone quality in these patients. In conclusion, as SLE patients are at risk for developing these two comorbidities (reduced vitamin D plasma levels and low BMD), it is essential to properly study, monitor, prevent and treat disorders of bone metabolism in SLE patients.

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