Introduction

In the field of rheumatic diseases there is growing evidence that vitamin D plays a relevant role in the pathophysiological mechanisms of autoimmunity. To this must be added that vitamin D deficiency in patients with rheumatic diseases is high. In contrast, there are few clinical trials demonstrating that vitamin D supplementation may contribute to the severity of the activity or the risk of systemic autoimmune diseases.

It seems that with the current schemes of vitamin D3 supplements, autoimmunity is not affected in the expected way\textsuperscript{1,2}, postulating that for the regulation of immunological homeostasis it is necessary to administer doses of vitamin D much higher than those used in standard clinical practice\textsuperscript{3,4}. There is no general consensus on what dose of vitamin D3 should be used, nor as to what levels of 25(OH) vitamin D (25HCC) –the metabolite that best reflects the vitamin D status of the organism– would be optimal to modulate favorably immunity or pain pathways.

As mentioned, most quality studies demonstrate a higher prevalence of 25HCC insufficiency in autoimmune rheumatic diseases\textsuperscript{5}. The causes of this insufficiency could be –in addition to the classic factors for the failure of 25HCC in the general population– others that are characteristic of rheumatologic autoimmune processes such as the use of corticosteroids, photosensitivity, cutaneous fibrosis and intestinal malabsorption, among others have not yet been fully elucidated\textsuperscript{5,6}.

Vitamin D3 could be one of the key factors that would act as an immunomodulator in the control of self-tolerance\textsuperscript{6}.

In Nordic regions, which are less exposed to ultraviolet radiation and consequently with lower levels of 25HCC, a higher prevalence of autoimmune diseases such as multiple sclerosis and inflammatory bowel disease has been described\textsuperscript{6,10}. However, in southern countries, where there is a high exposure to sunlight and one could expect sufficient levels of 25HCC, the high prevalence of vitamin D deficiency persists\textsuperscript{11,12}, despite the current supplementation guidelines which apply to many patients. Consequently, the existence of a possible malabsorption associated with the autoimmune disorder could be postulated\textsuperscript{13,14}. Finally, in relation to greater or lesser sun exposure, the seasonal factor in the development of some autoimmune diseases is a well-known fact\textsuperscript{15}.

Our objective is to review the main evidence on the role of vitamin D in autoimmune rheumatic diseases, osteoarthritis, and fibromyalgia.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is one of the most prevalent systemic autoimmune diseases. It is a chronic process and clinically courses with multiorgan involvement and periods of exacerbation and remission.

Age and sex matched studies revealed a higher prevalence of 25HCC insufficiency in patients with SLE in relation to the controls. Kamen et al.\textsuperscript{16}, in the Carolina Lupus Inception cohort, compared 240 healthy controls versus 124 SLE patients, determining a higher prevalence of 25HCC insufficiency in these patients. It reached up to 67%, a figure consistent with that published in other cohorts of patients with this same disease\textsuperscript{17,18}.

To date, the factors that have been associated with low levels of 25HCC in patients with SLE are: daily use of sun protection, elevated body mass index\textsuperscript{19}, use of glucocorticoids, seasonal change, serum creatinine\textsuperscript{20}, nephritis\textsuperscript{21}, altered protein/creatinine\textsuperscript{21}, low bone mineral density, fragility fractures\textsuperscript{22}, shorter telomere length in African American patients\textsuperscript{23}, lack of sun exposure and no treatment with hydroxychloroquine\textsuperscript{24}, a drug known to raise 25HCC levels at the expense of reduced levels of the active metabolite 1,25-DHCC.

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Recently, the presence of low levels of 25HCC has been associated with a higher prevalence of
classic cardiovascular risk factors such as hypertension and hyperlipidemia\(^a\), as well as with sleep disorders\(^b\) and fatigue\(^b\).

Many studies\(^d\)\(^e\)\(^f\)\(^g\), though not all\(^h\)\(^i\)\(^j\)\(^k\)\(^l\)\(^m\), have shown an association between 25HCC deficiency and increased SLE activity. It is important to emphasize that 4 of the 7 studies that did not find an association between 25HCC insufficiency and an increased SLE activity were performed in Spanish population groups\(^n\)\(^o\)\(^p\)\(^q\)\(^r\)\(^s\), so that certain sociodemographic, geographic and ethnic factors could influence this type of association.

On the other hand, low levels of 25HCC have been associated with fatigue and sleep disorders\(^d\)\(^e\). Fatigue is a symptom and therefore a subjective variable, difficult to quantify, but present in up to 90% of patients with SLE, with the consequent impact on their quality of life\(^q\). Fatigue has also been associated with low levels of 25HCC in Iranian nurses\(^s\), and these same findings have also been observed in other Spanish series of patients with SLE\(^t\)\(^u\). It is not known if the 25HCC insufficiency influences the level of fatigue in patients with SLE or vice versa. In 2016, Lima et al. carried out a placebo-controlled clinical trial in a young lupus population in which patients receiving vitamin D3 supplements improved the KSFS (Kids severity fatigue scale) scores when compared to the placebo group\(^v\).

Glucocorticoids are known to activate the destruction of 25HCC and 1,25DHC in inactive calcitriol acid. In 2010, Toloza et al. identified seasonal change, cumulative glucocorticoid dose and serum creatinine as factors associated with reduced levels of 25 HCC\(^w\). Recently, a significant correlation between failure of 25HCC and use of oral corticosteroids in women with SLE has been described in our country\(^x\). In fact, there was a positive correlation between the use of oral corticosteroids and the failure of 25HCC in patients who did not receive pharmacological vitamin D3 supplements, a fact that was not observed in the supplementation group\(^y\). At the European Rheumatology Congress (EULAR 2016), Lomarat W et al.\(^z\) presented a randomized, placebo-controlled trial where it was found that high-dose supplementation of ergocalciferol could serve as a safe adjuvant therapy generating a saving effect of corticosteroids in SLE patients (supplemented patients had used less oral prednisolone).

Therefore, patients with SLE are a high-risk group for vitamin D3 insufficiency. Thus, it is imperative to study, monitor, prevent and treat alterations of bone metabolism in them. In addition, pending the full results of the study by Lomarat W et al.\(^z\), it appears that vitamin D3 supplementation may reduce the use of corticosteroids. Given the benefit/risk profile, the possibility of supplementation with vitamin D3 as an adjuvant treatment in SLE should be considered.

**Systemic sclerosis**

Systemic sclerosis (SSc) is a connective tissue disease characterized by vascular obliteration, immune dysfunction, excessive deposition of the extracellular matrix and fibrosis of the connective tissue of the skin, lungs, gastrointestinal tract, heart and kidneys.

The prevalence of 25HCC insufficiency in SSc is high. According to Vacca et al., the figure was around 84% and the deficiency was 32%. 28% of patients had levels lower than 10 ng/mL\(^a\). These levels of insufficiency were associated with higher levels of disease activity and a higher negative correlation with ESR values, pulmonary fibrosis, and the value of the estimated pulmonary artery systolic pressure measured by echocardiography\(^b\), a poor prognostic factor. Arson et al. found lower 25-HCC levels in patients than in controls. They did not find statistically significant differences when comparing the SSc subgroup limited with diffuse SSc and between genders.

Additionally, Vacca A et al. found that supplementation with standard doses of vitamin D3 did not fully protect against the deficiency. There were also no differences in levels according to the types of SSc, limited or diffuse\(^a\).

In a multicenter study with 327 patients and 141 healthy controls, Arnesson et al. found a negative correlation between 25HCC insufficiency and disease severity, skin thickness and age\(^b\).

Caramaschi P et al. reported that patients with 25HCC deficiency had a significantly longer duration of illness from the first non-Raynaud symptom and that it was associated with a lower DLCO, an increased systolic pressure estimated in the pulmonary artery compared to the group in the range of failure\(^b\). They found no correlation with sex, age, antibody profile, cutaneous involvement assessed by the Rodnan score or presence or absence of digital ischemic ulcers\(^b\).

Humbert P et al. found that increased fibrosis of cutaneous tissue was correlated with low levels of 25HCC\(^b\).

Oral calcitriol supplementation in SSc showed positive cutaneous results in small open studies two decades ago\(^b\)\(^c\). Conversely, in a prospective, randomized, double-blind study, the effect of oral supplementation with calcitriol was no more effective than with placebo\(^b\).

Recently the expression of the vitamin D receptor (VDR) in fibroblasts of SSc patients and in murine SSc models was analyzed, appearing diminished. It was observed that VDR is a negative regulator of the TGF-β/Smad pathway such that poor signaling through poor cell expression and low levels of its specific ligand could contribute to hyperactivation of GFR leading to the aberrant activation of the fibroblasts\(^b\).

Cutaneous fibrosis plays a key role in the low levels of 25HCC both by inhibition of cutaneous synthesis and by malabsorption at the intestinal level. However, whether vitamin D3 deficiency in humans could perpetuate the mechanisms of fibrosis via the GFR-β/Smad pathway is insufficient in humans because of the impossibility of vitamin D3 deficiency for the down-regulation of this pathway and whether, in this case, high dose supplementation may have the expected effects.
Therefore, it seems that patients with SSc are at a high risk of vitamin D3 insufficiency. In an orphan disease of a therapy that modifies its clinical course, by the benefit/risk profile and cost/effectiveness, it would be prudent to recommend maintaining levels of sufficiency of 25HCC. It is unclear what supplement dosages would be adequate to achieve this goal, as well as the delimitation of optimal levels to be reached in blood to obtain the greatest clinical benefit. Higher quality clinical trials should be conducted to decide which doses are appropriate.

**Sjögren’s syndrome**

Sjögren’s syndrome (SS) is a systemic autoimmune disease characterized by a chronic inflammation of the exocrine glands mainly salivary and lacrimal glands. Xerostomia and keratoconjunctivitis sicca are the key clinical elements.

A recent study reported that 25HCC levels were significantly lower in patients with primary Sjögren’s syndrome than in the general population. This difference was significant in women but not in men.

Baldini et al. assessed the prevalence of the 25HCC deficiency, concluding that it is associated with an early stage of the disease, not being related to the activity of the process or to glandular or extra-glandular clinical manifestations.

Agmon-Levin et al. replicated the study with a greater number of cases and controls, and demonstrated that 25 HCC levels were comparable between patients with primary SS and healthy controls. Importantly, their research also revealed that low levels of 25HCC correlated with the presence of peripheral neuropathy and lymphoma, an association that has been studied by other authors. Thus, for example, 125DHCC has been reported to have an antiproliferative effect resulting in tumor regression in low grade non-Hodgkin follicular lymphomas of malignancy.

Lee SJ et al. investigated the association between disease activity and serum levels of 25HCC. Included in this study were 69 patients with primary SS and 22 controls. These investigators concluded that serum levels of 25HCC were significantly lower in patients with SS syndrome compared to controls matched for age and sex. When assessing the activity with EULAR Sjögren’s syndrome disease activity index (ESSDAI) found a negative association with 25HCC levels.

With the data available today, we can state that there is insufficient vitamin D3 in MCTD. There are no clinical trials that have investigated the role of supplementation over the clinical course and disease activity, so it would be prudent to conduct quality clinical trials to discern their role in this pathology. As practical clinical advice, we believe it judicious to keep patients at sufficient 25HCC levels.

**Spondyloarthropathies**

Spondyloarthropathies are chronic inflammatory arthritis, autoimmune rachis, spinal, and especially sacroiliac joints, which are characterized by sharing the same symptoms and therapeutic responses. In some cases, they are associated with HLA B27. These include: ankylosing spondylitis, psoriatic arthropathy, arthritis associated with inflammatory bowel diseases, reactive arthritis and undifferentiated spondyloarthropathies.

Cross-sectional studies show that 25HCC insufficiency is more frequent in patients with spondyloarthropathies compared to the general population. Recently published data from the DESIR cohort was 11.7%, compared to 5% in the control population. In addition, they suggest an inverse correlation between 25HCC levels, activity, radiological progression, and increase of acute phase reactants. They describe a higher percentage of patients with severe 25HCC deficiency in early axial spondyloarthritis, associating the 25HCC deficiency with an increased activity and severity of the disease as well as the presence of metabolic syndrome.

Ertén et al. describe an increased 25HCC deficiency in male patients with ankylosing spondylitis as well as an inverse correlation with acute phase reactants.
In spondyloarthropathies, two opposing effects on bone metabolism have been described: on the one hand, an increase in osteoporosis and the prevalence of vertebral fracture related to trabecular bone resorption induced by the RANK-ligand positive regulation pathway. On the other hand, an increase of bone formation in the enthese through morphogenic bone proteins, TFG-β, and positive regulation of the Wnt pathway.

In vitro studies demonstrate that vitamin D3 interferes with the molecular pathways of inflammation and ossification at the level of enthese, mainly at the level of IL-23 and increasing sclerostin (Wnt inhibitor). Saad et al. reported that serum levels of sclerostin (Wnt inhibitor) increased significantly after one year of treatment with anti-TNF, also improving bone mineral density of the lumbar spine.

In their study, Appel H et al. determined that serum levels of sclerostin were significantly lower in patients with ankylosing spondylitis (AS) than in healthy controls. Thus, low levels of sclerostin were associated with the formation of syndesmophytes, emphasizing the role of sclerostin in the suppression of bone formation at this level in spondyloarthropathies.

In addition, vitamin D3 insufficiency may also be related to intestinal inflammation and malabsorption in spondyloarthropathies. Therefore, insufficient 25HCC levels have been reported in spondyloarthropathies that appear to correlate with increased disease activity. Supplementation with vitamin D3 could represent a therapeutic adjuvant pathway in this pathology. But quality clinical trials with vitamin D3 supplementation that take into account all the variables that may influence are necessary to discern the complex relationships between 25HCC insufficiency and spondyloarthropathies.

**Rheumatoid arthritis**

Rheumatoid arthritis (RA) is an autoimmune systemic inflammatory disease, characterized by persistent inflammation of the joints, which typically affects the small joints of the hands and feet, causing their progressive destruction and generating different degrees of deformity and functional disability. Autoimmunity plays a major role in its origin, its chronicity and the progression of the disease. The disease is associated with the presence of autoantibodies (rheumatoid factor and citrullinated cyclic antibodies). Sometimes, it also manifests with extra-articular manifestations.

As in the rest of the systemic autoimmune diseases, the 25HCC insufficiency in patients with rheumatoid arthritis is higher than in the general population. Kerr GS et al. estimated the prevalence of 25HCC insufficiency in 84% of their series, while the prevalence of 25HCC deficiency was estimated in 45% of their patients. According to Gopinath et al., the prevalence of the 25HCC deficiency was 68.1%.

The onset, severity and outbreaks of rheumatoid arthritis have been described as seasonally dependent. For example, Mouterde et al. suggested that patients who experienced the first symptoms of rheumatoid arthritis in winter or spring had a more severe progression of joint damage at 6 months than patients who experienced the first symptoms in the summer.

Merlino LA et al. linked 25HCC insufficiency in Caucasian patients, with an increased risk of disease development and increased disease activity. In their series with 76% of Caucasian patients, Kerr GS et al. found a significant link between deficiency and failure of 25HCC for the anti-CCP positivity in non-Caucasian patients. The deficiency, but not 25HCC insufficiency, was associated with a greater number of painful joints and higher values of high C-reactive protein. In contrast to European cohorts, Craig SM et al. did not find associations with the disease activity in African-American patients. Significant clinical improvement was correlated with the immunomodulatory potential of 1,25-DHCC.

To date, there are only three clinical trials that assess the efficacy of vitamin D3 supplements and disease activity. In the open-label trial by Salesi and Farajzadegan, comparing patients on triple immunosuppressive therapy and supplementation with 1,25DHCC versus triple therapy alone, patients showed greater pain relief without any effect on disease activity. In another randomized double-blind trial with methotrexate at steady-dose and supplementation with 25HCC 50,000 IU weekly versus methotrexate at steady-dose and placebo, there were no improvements in efficacy results. Nor did supplements have the expected effect in a double-blind controlled trial in which supplements were given with 25 HCC 50,000 IU 3 times per week for 4 weeks and then 50,000 IU twice monthly for 11 months, with no improvement in disease activity or in measurements of bone mineral density and increasing levels of TNF-alpha in the supplemented group. In the same line, Dehghan et al. concluded that 25HCC insufficiency is not a risk factor for increased disease activity, nor does it have an impact on the number of outbreaks.

With these results, patients with rheumatoid arthritis could be considered a high risk group for vitamin D3 insufficiency, so it is necessary to study, monitor, prevent and treat alterations of bone metabolism in patients who already present an independent risk factor for osteoporosis. There is insufficient evidence to recommend treatment at high doses of vitamin D3 in search of a potential immunosuppressive effect.

**Arthrosis**

Osteoarthritis or arthrosis is a chronic non-inflammatory disease caused by progressive wear of cartilage and joints. The affected joints cause pain, lose mobility and become deformed. It is the most frequent rheumatic disease, especially among the elderly. Observational data have suggested an association between low levels of 25HCC, pain and
radiographic changes in osteoarthritis81.82. A cross-sectional analysis of data from the Hertfordshire cohort suggested that 25HCC may be associated more to pain than to radiographic change83. The prospective study of the Framingham cohort concluded that low serum levels of 25HCC may be associated with an increased risk of osteoarthritis of the knee84. A recent prospective observational study demonstrated that vitamin D3 deficiency independently predicts the onset or worsening of knee pain in the next 5 years, and of hip in the following 2.4 years. Based on this association, it has been suggested that correction of 25HCC deficiency may reduce the worsening of knee or hip pain in the elderly, but supplementing those without non-deficiency would probably be ineffective85.

However, two randomized clinical trials of vitamin D3 supplementation have found no benefit in this approach86,87, although another trial reported a small degree of symptomatic improvement88.

In the largest and most recent of these randomized controlled trials89, 413 patients with symptomatic knee osteoarthritis and low levels of 25HCC participated. Supplementation with cholecalciferol (50,000 IU administered orally monthly) showed no significant difference compared to placebo in both knee pain and volume of the tibial cartilage measured by magnetic resonance at two years89. On the other hand, McAlindon et al. had obtained similar results in a previous study recruiting 146 patients who randomized cholecalciferol supplementation to 2,000 IU/day (with dose escalation if 25HCC levels remained below 36 ng/ml) or placebo. After 2 years of supplementation, when comparing the two groups, there was no difference either in pain or in the volume of cartilage lost89.

Sanghi D et al. recruited 106 randomized patients to receive 60,000 IU per month of 25HCC or placebo and found a small but statistically significant improvement in pain and function. However, the differences in this study were 1 mm in the visual analogue scale and 2 in the WOMAC questionnaire90.

Therefore, although vitamin D levels appear to be lower in the arthritic population than in the general population, the possible role of vitamin D3 in treating osteoarthritis is not entirely clear. Future studies are required with larger sample sizes, longer follow-up and probably higher doses of supplementation. Based on current evidence, it cannot be concluded that there is benefit for the arthritic population when treated with high doses of vitamin D3.

Fibromyalgia
Fibromyalgia is part of central sensitization syndromes. Its main symptom is chronic, generalized musculoskeletal pain with a wide variety of accompanying symptoms, mainly cognitive (difficulty concentrating, sleep disturbances, anxiety, depression), fatigue, irritable bowel, sleep disturbances and bruxism.

Current therapeutic approaches for patients with fibromyalgia have a multidimensional nature, which includes patient education, behavioral therapy, exercise, pain management and relief of chronic symptoms, rather than mechanisms based pharmacological therapies Pathophysiology of the disease91.

Vitamin D is assumed to play a role in regulating the processing of chronic, widespread pain in fibromyalgia through complex central and peripheral interactions, so its deficiency could result in an amplification of pain signals. The presence of the vitamin D receptor (VDR) and the 1-alpha hydroxylase and the vitamin D binding protein (VDBP) in the hypothalamus is suggested as a mechanism.

Some, but not all, observational studies report that 25HCC insufficiency is more common in fibromyalgia patients than in the general population. However, this association may be due to the existence of concomitant confounding factors, such as physical inactivity, obesity or depression92,93.

To date there is only one randomized placebo-controlled clinical trial in patients with fibromyalgia92. Wepner F et al. included 37 women and 3 men whose serum levels of 25HCC were less than 32 ng/ml. Patients were randomly assigned to receive 25HCC or placebo for 20 weeks. The supplemented group received 2,400 IU/day if they presented deficiency levels and 1,200 IU/day if they were in levels of insufficiency, with the objective of reaching serum levels of 25HCC between 32 and 48 ng/ml94. In post hoc sub-analysis, significant results were found regarding pain improvement and functionality in patients who normalized the levels of 25HCC94.

However, we have two randomized, placebo-controlled clinical trials in patients with non-specific generalized chronic pain95,96,97, and several uncontrolled trials with multiple bias98,99, both in patients with non-specific generalized chronic pain95,96,97 and with Diagnosis of fibromyalgia98,99. From their analysis, most of the potential benefits of treatment with vitamin D3 on the pain and severity of the disease seem to be concluded.

Warner et al. contradict this possibility in their research97. Although methodologically they had a placebo control group, as in the rest of the studies, there are biases to consider. Patients included had a mean age of 60 years. Patients with levels below 9 ng/ml were excluded and supplementation was performed with ergocalciferol. In addition, the study was performed in summer, which would justify an improvement in the placebo group97. On the other hand, in the most recent uncontrolled trials96, which included patients with non-specific generalized chronic pain (50% met fibromyalgia criteria), patients with 50,000 IU/week of oral 25HCC were supplemented for 3 months, with no control group. The authors reported improvements in musculoskeletal symptoms, depression level, and quality of life96.

In the results of the European Male Ageing Study cohort, male patients included with non-specific generalized chronic pain had lower levels of 25HCC than those without pain. It was conclu-
ded that the 25HC deficiency increased the risk of suffering generalized non-specific chronic pain by 50% (20). After a follow-up period, those patients who had levels below 15.6 ng/dl had a significantly increased risk of developing non-specific generalized chronic pain (20). On the other hand, a cross-sectional study with 75 patients demonstrated a relationship between 25HC deficiency and anxiety or depression (21). Therefore, patients with fibromyalgia are a high-risk group for vitamin D3 deficiency, particularly those with smoking and/or drinking and obesity and/or depression (21), so it would be prudent to keep these patients at levels of 25HC sufficiency to minimize the risk of osteoporosis and maximize muscle strength. Given the current evidence, it is not possible to say whether vitamin D3 supplements may improve pain and function in these patients, and therefore more randomized, double-blind, and minimal-bias clinical trials are needed to provide high-quality evidence on this hypothesis.

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**Bibliography**


15. Haase RT, Awad KS, AB MK, Hamed AJ. Reduced serum concentrations of 25-hydroxy vitamin D in Egyptian


59. Kim HR, Kim HY, Lee SH. Elevated serum levels of soluble receptor activator of nuclear factor-κB ligand (sRANKL) and reduced bone mineral density in patients with ankylosing spondylitis (AS). Rheumatology. 2006;45:1197-200.


