

**Effect of Vitamin D supplementation on Systemic Lupus Erythematosus****Efeito da suplementação de Vitamina D no Lúpus Eritematoso Sistêmico**

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**Adrielly Maria Duque de Siqueira**

Barachel em Biomedicina pelo Centro Universitário UNIFAVIP | Wyden

Instituição: Centro Universitário UNIFAVIP | Wyden

Endereço: Avenida Adjar da Silva Casé, 800 - Indianópolis, Caruaru - PE, Brasil

E-mail: adiellysiqueira.37@gmail.com

**Pâmella Grasielle Vital Dias de Souza**

Doutora em Bioquímica e Fisiologia, pela Universidade Federal de Pernambuco

Instituição: Universidade Federal de Pernambuco (UFPE)

Endereço: Av. Prof. Moraes Rego, 1235 - Cidade Universitária, Recife -PE, 50670-901

E-mail: pamella.souza@unifavip.edu.br

**ABSTRACT**

Autoimmune disorders are chronic diseases characterized by loss of tolerance of the immune system, resulting in major problems in the normal functioning of the body. Among the autoimmune diseases, systemic lupus erythematosus (SLE) has received a great deal of attention given the complexity of the disease, which affects multiple organs and tissues. Among existing treatments vitamin D supplementation is being considered as a new form of treatment given the effects that vitamin D has on the immune system. Vitamin D is well known for its effects on calcium regulation and its role in metabolic processes, but research has shown that this vitamin has a pluripotent effect on many systems, including immune cells. In this context, the present study aims to relate clinical and laboratory characteristics with the presence of vitamin D supplementation in these patients. This study allowed us to draw a clinical and laboratory profile of patients with SLE positive for vitamin D supplementation. Finally, this review provided a better direction of therapy for patients diagnosed with SLE through vitamin D supplementation. as well as demonstrating the importance of adequate serum vitamin D levels for humans, for the overall functioning of the body.

**Keywords:** Doença Pulmonar Obstrutiva Crônica, Reabilitação, Teste de Caminhada de 6 minutos.

**RESUMO**

As patologias autoimunes são doenças crônicas que se caracterizam pela perda da tolerância do sistema imunológico, resultando em grandes problemas no funcionamento normal do organismo. Dentre as doenças autoimunes, o lúpus eritematoso sistêmico (LES) vem recebendo um grande destaque visto à complexidade da doença, que afeta múltiplos órgãos e tecidos. Dentre os tratamentos existentes a suplementação de vitamina D está sendo considerada como uma nova forma de tratamento visto os efeitos que a vitamina D possui no sistema imunológico. A vitamina D é bastante conhecida pelos seus efeitos na regulação do cálcio e sua atuação em processos metabólicos, porém pesquisas demonstram que esta vitamina possui um efeito pluripotente em vários sistemas, inclusive nas células imunológicas. Neste contexto, o presente estudo visa

relacionar as características clínicas e laboratoriais com a presença da suplementação de vitamina D, nestes pacientes. Com este estudo permitiu-se traçar um perfil clínico-laboratorial de pacientes com LES positivos para a suplementação de vitamina D. Por fim, essa revisão permitiu propiciar um melhor direcionamento da terapêutica para os pacientes diagnosticados com LES, através da suplementação de vitamina D, bem como demonstrar a importância dos níveis séricos adequados de vitamina D para o ser humano, para um funcionamento de modo geral do organismo.

**Keywords:** Lúpus Eritematoso Sistêmico, vitamina D, deficiência, efeito.

## 1 INTRODUCTION

The systemic lupus erythematosus (SLE) is an inflammatory autoimmune chronic disease that affects organs and tissues, oscillating between exacerbation and remission. Famous for autoantibodies' production, responsible for the organs and tissue damage, as well as the loss of self-tolerance.<sup>1</sup>

Amongst the existing causes which can set SLE in action are included: genetic, environmental, hormonal, and immunological factors. According to the Brazilian Health Ministry, SLE affects all races. Still, its' seen a predominance in women of reproductive age, signs, and symptoms such as fatigue, joint pain, skin rash, fever, and photosensitivity. It can also cause injuries in several organs, kidneys essentially, inducing acute glomerulonephritis, being not only a source of physical disability but also threatening the patient's life.<sup>2</sup>

Currently, the treatment of SLE is arranged individually, making usage of medicine that regulates the immune system, including corticosteroids, immunosuppressants, antimalarials and, also the sunscreen daily use. Depending on the disease liveliness, the use of anti-inflammatory drugs is also necessary.<sup>3</sup>

Recently, researchers have been investing in vitamin D supplementation as a new treatment approach, as studies prove the importance of an ideal parameter of this vitamin in SLE patients.<sup>4</sup>

According to Souza,<sup>5</sup> there are several studies on vitamin D deficiency in SLE patients, demonstrating photosensitivity as a disease aspect, which consequently leads to its absorption decrease. As these patients have photosensitivity, they end up exhibiting low levels of the body's available vitamin D, since its greatest form of absorption is through sunlight exposure.

Calciferol (vitamin D synonym) is well known for the calcium hemostasis management, a discovery worth the Nobel Prize in 1938. Even so, its effects go far beyond calcium use maintenance. This vitamin has a pluripotent impact on various tissues. It can also be considered as a pre-hormone, since its formation occurs when exposed ultraviolet B radiation, being produced in an endogenous way in the cutaneous tissues, plus it can be absorbed through diet as well.

However, alone, it represents a limited absorption, its active form in the body is found as 25 (OH) D.<sup>6</sup>

Several studies have reported the vitamin D interaction with the immune system. This relation occurs for this vitamin influences and differentiates cells of myeloid and lymphoid origin, for instance, T and B lymphocytes, macrophages, and Natural Killer cells; it still may modify the interleukins production, operating both in defense and adaptive response. These factors motivate the believing that when vitamin D has low serum levels, it contributes to a failing immune system regulation and in patients who show genetic predisposition, this deficiency can act as an environmental factor that triggers autoimmune diseases, as well as stimulating a disease liveliness that could be in remission.<sup>7</sup>

Vitamin D supplementation in these subjects is being considered as a treatment method to improve the immune system coordination and to decrease the inflammatory status. Moreover, it is important to search for new studies that demonstrate the therapeutic risks, benefits, and the precaution that the vitamin D supplementation can furnish to SLE patients, likewise its impacts on this population.<sup>8</sup>

## **2 MATERIAL AND METHODS**

A systematic and discerning evidence investigation was carried out among February and October 2019, on BIREME, PubMed, LILACS, SCIELO, and EBSCO online platforms. This examination prioritized studies published in the last 12 years (2007-2019), concerning the correlation of vitamin D reinforcement and SLE control. This study's mission was to collect and incorporate research results in a well-organized process, and as the data source, the chosen literature itself, performing an impartial and combined statement, and still to acknowledge the quality and agreement between the obtained results.

To precisely define the literature adequacy as a base for this study review, the following inclusion criteria were determined: a) articles with human beings; b) articles published in the past 12 years (2007—2019); c) patients of both sexes; d) studies published in English, Portuguese or Spanish. The exclusion measures are provided to exclude the studies that did not apply to the parameters listed before in their methodology, and that did not include the descriptors: SLE; D vitamin; deficiency; effect. These keywords were used individually or in combination.

In the initial search 510 articles were selected, and after being filtered by the inclusion and exclusion criteria, 33 articles. The study selection process took place individually, with two other

meetings being held with the additional authors. One after the screening, and the other, after applying the eligibility criteria to collectively determine the articles to be included.

### **3 RESULTS AND DISCUSSION**

This study was noted a meaningful increase in the number of studies about the prevalence of the of vitamin D supplementation use in SLE, obtaining more than twice the number of studies included in the previous review. The selected articles were arranged in five classes: a) Pathophysiology of SLE; b) World mortality due to SLE; c) Prevalence of vitamin D deficiency in SLE; d) Incidence of SLE activity in patients with vitamin D deficiency; e) Effectiveness of vitamin D supplementation in patients with SLE. This action aimed to satisfy the research objectives.

#### **3.1 PATHOPHYSIOLOGY OF SYSTEMIC LUPUS ERYTHEMATOSUS**

In this section, 8 articles were selected which revealed that SLE is a complex disease, and may be linked to the ailment of multiple organs, often leading the patient to have an unstable and risky life when the condition is not stabilized.

The systemic lupus erythematosus (SLE) is an inflammatory and chronic ailment, autoimmune nature, responsible for affecting various organs and tissues. It emerges in periods of activity and remission.<sup>9</sup> Its etiology is multifactorial. However, there are genetic, environmental, and hormonal factors proving to be quite relevant in its cause inducing the immune system irregularity in the autoantibodies production, as it strikes itself origin and leads to tissue damage.

<sup>10</sup>

According to the Souza et al., (2010) study,<sup>11</sup> the immune system irregularity of these patients points to the production of divergent auto-reactive antibodies. These antibodies react with nuclear components, particularly the DNA ribonucleoproteins, the histones, and antigens existing in the nucleoli. The immune complexes formed by the auto-reactive antibodies and the specific antigens, remain in the blood circulation, and consequently are stored in the skin, the blood vessels, and the renal glomeruli, causing the entire inflammatory process.<sup>12</sup>

The signs and symptoms of SLE include: renal, cardiac, hematological, joint, neurological involvement, the same as the presence of fatigue, fever, and photosensitivity. Thusly undermining the life quality of these individuals, enhancing the decease occurrence. The determination of which organs will be affected is determined by the deposition place of the formed immune complex.<sup>13</sup>

The signs and symptoms of SLE are the immune system malfunction reflections that begins to produce the autoantibodies. Hence, the individual diagnosed with this pathology displays the following signs: severe joints pain, weight and hair loss, kidney complications, edema, Raynaud's phenomenon, and the presence of skin rash commonly known as butterfly. <sup>9</sup>

The laboratory diagnosis is executed by immunological tests that show an incidence of 94% in SLE cases, known as the anti-core factor (FAN), anti-D antibody, anti-Sm antibodies that result in positive only for SLE patients, anti-SSA, and anti-SSB. In addition to the aforementioned tests, there are complementary experiments like complete blood count, urine summary, c-reactive protein, and tests that establish the evidence about the quality of kidney capacity and supports a more precise examination. <sup>14</sup>

These patients' treatment relies upon the type of manifestation displayed and must be done in an individualized way. The medicine includes prescriptions that adjusts the immunological changes and the fluctuations caused by the inflammatory condition. <sup>15</sup>

It is crucial to consider protective measures towards the solar radiation. As the exposure to ultraviolet rays issues the immune system, it promotes the formation of immune complexes that can trigger organs inflammation, so as kidneys, and also worsening the photosensitivity framework. The physical activity practice is also indicated, for it can contribute to stabilizing blood rates as glucose for example. Trying as much as possible to have a peaceful lifestyle, avoiding stress can improve the immune system, for it suffers deregulatory effects in uneasy situations. <sup>16</sup>

### 3.2 SLE WORLD MORTALITY

In the SLE worldwide mortality category, 5 articles were found. The mortality rate of SLE patients in Brazil is 4.76 deaths / 100,000 inhabitants with women as the majority. It is believed that this leading quantity happens regarding the fact that women at childbearing age have a higher production of hormones often responsible and also undoubtedly influences antibodies production, consequently, the woman's body is extra susceptible to immunological changes. <sup>17</sup>

The disease mechanism causes a vulnerability to infections due to the immune system failure, resulting in clinical condition complications. The commonly used treatment with glucocorticoids has anti-inflammatory and immunosuppressive effects, the intensity of these effects is equal to the amount of dosage, and treatment period. Being uncertain whether the long-term effects of these medications are considered safe. <sup>3</sup>

It is established that such medicines may cause adverse effects as an example reducing intestinal calcium absorption, minimizing the effects of vitamin D, promoting calciuria (when calcium in excess detected in the urine excretion), and also leading to secondary hyperparathyroidism. The final effect of this chain of events may still be responsible for the onset of osteopenia and osteoporosis. Therefore, its use requires to be proper and meticulously evaluated.<sup>18</sup>

Among the reviewed studies, it was perceived cities with lowest municipal human development rates in the country are located in the North and Northeast Brazilian regions, this stated, SLE patients who live in emerging countries like Brazil have a worse prognosis. This evidence might relate to the low socioeconomic and educational level, contributing to the diagnosis delay, and hard access to health services.<sup>17</sup>

Most Brazilian studies are restricted to the Southeast Region. In one of these examinations carried out in other Brazilian regions, it was plausible to recognize that in this analysis of 63 patients supervised in the State of Paraíba, Northeast region, had established a connection between the poorest life quality, measured at the study inception, and a greater risk of passing. Revealing that less developed regions have a predominance of SLE fatal cases.<sup>19</sup>

Other analyses performed in Morocco reported that the epidemiology of SLE in developing countries is still unknown and is underestimated, which makes the comparison challenging to other international data.<sup>20</sup>

### 3.3 PREVALENCE OF VITAMIN D DEFICIENCY IN SLE

In this context, 8 articles were selected. From those it was possible to analyze that vitamin D deficiency manifests in about 80% of SLE patients, and these patients also have several factors that lower its absorption such as photosensitivity, identified as its most common clinical indication.

When SLE patients expose themselves to ultraviolet rays it leads to a divergent auto-reactive antibodies production, then they react with the nuclear components, mainly the DNA, histones, and antigens, found in the nucleoli. Ensuring the immune complexes deposition and consequently culminating the inflammatory response, leading to vitamin D deficiency.<sup>12</sup>

This vitamin body's activation process, is through ultraviolet B rays exposure, right after the vitamin D is transported to the liver undergoing hydroxylation, being converted into 25-hydroxyvitamin D [25 (OH) D], circulating in greater profusion, yet inactive. The final stage of

this hormone production is the additional hydroxylation that takes place in the kidneys, originating the 1,25 dihydroxy vitamin D [or 1,25(OH)<sub>2</sub> D<sub>3</sub>], now in its active biological form.<sup>21</sup>

In such a way, it is noticeable that these patients end up developing vitamin D deficiency more often compared to other patients, and as before said, resulting in exacerbations in the clinical picture, for vitamin D acts in several systems, including the immune system.

The cases are classified as insufficiency when the values are underneath 30ng / mL, and deficiency when inferior to 20ng / mL are detected. Reports pointed out that SLE patients had lower values compared to control patients. Some articles suggest that the vitamin D level detected in these patients is higher than 80ng / mL so, it is possible to obtain a good immune system function while other pieces report that this parameter is not yet well defined. However, both agree that the vitamin D value in SLE patients must be different from what is required to prevent deficiency or calcium homeostasis maintenance.<sup>22</sup>

The vitamin D is quite involved in immunological responses, both the innate and adaptive. Some articles report that SLE patients who had vitamin D deficiency demonstrated an increase in both lymphocytes count and the interleukin concentration, contributing to the patient preservation in the inflammatory state.<sup>7</sup>

In case study reports, it was able to certify an 81.6% prevalence of SLE patients, whose values were under the normal vitamin D scale.<sup>8</sup> Fragoso (2012), presented the insufficiency/deficiency of 25(OH)D in 45 (57.7%) SLE patients and in 25 (39%) individuals in the comparison group, thus reinforcing the prevalence of SLE patients with vitamin D deficiency.<sup>23</sup>

A study pulled out in Mexico with 137 SLE patients showed that 83% of the patients had vitamin D insufficiency, exhibiting more significant data in the matter.<sup>24</sup> In his studies with children and adolescents, being 30 test patients and 30 control patients, Peracchi could indicate that 29 test patients had serum concentrations inferior to the reference value. Therefore, it is perceivable that the studies conferred a predominance of vitamin D deficiency in patients with SLE, emphasizing that vitamin supplementation might be a great ally in the treatment, making it possible to analyze the parameter of how the patients are most likely to develop deficiency/insufficiency.<sup>25</sup>

### 3.4 VITAMIN D SUPPLEMENTATION EFFECT ON SLE

In this subject were selected 5 articles, and from them was possible to state that vitamin D has an important effect on the immune system, for its' connection to several immune responses.

This association occurs because this vitamin acts in the immune cell regulation and differentiation. For example, the T and B lymphocytes, macrophages, natural killer cells (NK), and it can also interfere in the interleukins production, that said, vitamin D plays an important role in the innate and adaptive immune response regulation.<sup>7</sup>

Vitamin insufficiency in the body may increase innate immunity and decrease adaptive immunity, affecting the formation of T lymphocytes, leading to an immune response inaccuracy, leading to intolerance. As for B cells, vitamin D deficiency decreases the antibodies secretion and increases the production of autoantibodies.<sup>26</sup>

Previously, another evidence that strengthens the vitamin D role in the immune system activation is due to its identification receptors in several cells in the immune system, including T lymphocytes, B lymphocytes, and dendritic cells. Therefrom, vitamin D is being studied as an immunoregulatory factor. In lymphocytes, the main actions of vitamin D consists in altering the secretion of pro-inflammatory cytokines, and the reduces the Interferons-Gamma (IFN- $\gamma$ ) and Interleukins-2 (IL-2) following to a weakened ability to present antigens to the lymphocytes, and also modifies the activation and clonal expansion of the before-mentioned cells. At the same time the IL-4, IL-5, and IL-10 production increases and modifies the T helper cell phenotype, evoking a immunological inflammatory tolerance. In such a way, developing an immune response profile with reduced inflammatory reactions.<sup>27</sup>

It has been mentioned that the expression of regulatory T cells increases when vitamin D is present, and these cells are distinguished by secreting IL-10 and preventing the autoimmune diseases progress. The B lymphocytes are also the target of vitamin D action, with direct effects such as stimulating apoptosis and preventing cell maturation, which may outcome in self-tolerance.<sup>4</sup>

The aforementioned factors lead to admitting that when there is low vitamin D levels in the body, it results to an immune system regulation failure and in cases with patients genetically predisposed, the vitamin can act as an environmental factor triggering autoimmune diseases, and also inducing the disease activity, that could be in remission.<sup>24</sup>

### 3.5 VITAMIN D SUPPLEMENTATION EFFICIENCY IN SLE PATIENTS

In supplementation matter, 6 articles were chosen. From them was possible to explore a study with 171 SLE patients, and this study objective was to investigate the presence of anti-vitamin D antibodies, aiming to properly explain vitamin D deficiency in autoimmune diseases describing that 4% of SLE patients had the antibody. Yet, the researchers believe that such



antibody plays a significant role in vitamin D deficiency, by using it as a diagnosis and prognosis biological marker.<sup>28</sup>

Another study estimates the prevalence of vitamin D deficiency or insufficiency in Korean SLE patients. The relation between vitamin D levels and the SLE activity markers, and the use influence of corticosteroids on vitamin D depletion was analyzed, but they did not find meaningful results involving SLE activity. Though, the vitamin D serum levels in these patients were significantly lower than in control patients.<sup>29</sup>

In the study by Kamen and Oates in 2017, the participants received daily vitamin D3 oral doses. Group 1 (control) received 400 IU of vitamin D3 daily, and Group 2 (treatment) received 5,000 IU. At the study's end they stated a remarkable improvement in the endothelial function when comparing groups 1 and 2.<sup>30</sup> Another study measured vitamin D serum levels and evaluated SLE activity and fatigue, where the research participants received oral supplementation, 50.000 IU per week or placebo. When the treatment ended, it was clear that vitamin D supplementation was effective in decreasing SLE activity and preventing the fatigue symptom in juvenile patients.

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The results written by Petri et al. in 2017 when evaluating 763 North American SLE patients, registered that individuals with low vitamin D levels when supplemented with 50.000 IU of vitamin D2 weekly, and with 200 IU of Ca / D3, twice per day for 128 weeks, manifested at the conclusion a balance in serum vitamin D values, including a reduction in the elevated disease activity risk, decreasing the inflammatory mediators.<sup>32</sup>

Terrier et al. (2012), found a meaningful development of 25 (OH) D serum levels and regulatory T cells in 20 French patients with D hypovitaminosis after the supplementation program of 100,000 IU cholecalciferol / 4 weeks, followed by 100,000 IU cholecalciferol/month for six months. There was also a decay in B memory cells and T effector cells effectiveness, therefore, inducing the immunomodulatory effect in SLE, emphasizing the participation of anti-vitamin D antibodies in its metabolic process it is possible to observe that the vitamin deficiency remained once more present, in addition to immune cells changes and the participation of anti-vitamin D antibodies contributing to an atrophy in the vitamin absorption.<sup>33</sup>

#### **4 CONCLUSION**

The approach on the vitamin D effect on SLE is extremely relevant, so health specialists may offer a better direction in Public Health Policies aimed at these patients. It is also worth

mentioning that there are few studies about the Brazilian population, requiring a greater number of studies to understand the vitamin effects on SLE in this territory.

This research focused on the vitamin D supplementation effect on SLE, and it can be verified that from this research it was verified that there is a prevalent association in SLE patients who develop vitamin D deficiency, affecting several organism functions of these patients centered in the inflammatory issue of SLE activity, which resembles the basis for the clinical picture. Also being able to include the vitamin D supplementation benefits for these patients may allow subsidies for the implementation of a unified and consistent treatment, improving the standard of living through a method of easy access.

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