



## Editorial

### Vitamin D and autoimmune rheumatic disease<sup>☆</sup>



### Vitamina D y enfermedades autoinmunes reumáticas

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In recent decades, a great deal of attention has been focused on vitamin D because of the discovery of its immunoregulatory properties, by which it contributes to self-tolerance and improves the innate immune response to microorganisms. It has been proposed that, being a secosteroid, vitamin D could reduce the immunological response in a way similar to the steroids.<sup>1</sup> Clinical, epidemiological and experimental studies demonstrate the potential role of vitamin D in the development and perpetuation of different autoimmune diseases, such as systemic lupus erythematosus (SLE), type 1 diabetes mellitus (T1D), multiple sclerosis (MS) and rheumatoid arthritis (RA).<sup>2</sup>

The cornerstone of immunoregulation by this vitamin is the vitamin D receptor (VDR), which is present in several cells of the immune system. The binding of 1,25(OH)<sub>2</sub>D<sub>3</sub> to the receptor induces an improvement in phagocytosis and a decrease in the expression of major histocompatibility complex class II DR in dendritic cells, as well as a decrease in the expression and response of costimulatory molecules that regulate the maturation and migration of these cells, blocking their final differentiation. Other actions are the induction to maturity of natural killer (NK) cells and of TCD4+CD25+Foxp3 cells (regulatory T cells or Tregs) capable of mediating immune tolerance and, in consequence, reducing the development of autoimmune disorders; and decreasing the differentiation and proliferation of B lymphocytes to plasma cells and their apoptosis. Regarding its action on inflammatory cytokines, it reduces the production of the proinflammatory cytokines IL-17A, IL-17F, IL-22, IL-23, IL-12, IL-2, IL-6, tumor necrosis factor alpha (TNF $\alpha$ ) and interferon  $\gamma$  (IFN  $\gamma$ ); at the same time, it increases the production of the anti-inflammatory cytokines IL-10 and transforming growth factor beta (TGF $\beta$ ).<sup>3–10</sup>

The molecular mechanism by which the vitamin D/VDR interaction functions involves interfering with the nuclear factor of activated T cells (NF-AT) and with the nuclear factor of  $\kappa$ B (NF- $\kappa$ B), as well as directly modulating the promoter regions in the genes of different cytokines.<sup>11</sup> Moreover, it increases the IL-4

concentration,<sup>12</sup> and the mRNA of IL-2, as well as that of cytokines produced by the Treg cells (CD4+CD25+); the expression of Toll-like receptor 4 (TLR4) is also notable.<sup>13,14</sup> These are the most important mechanisms that indicate the protective capacity of vitamin D against autoimmunity.

The serum vitamin D concentration depends on several factors: sunlight exposure, age, ethnicity, body mass index and use of drugs (steroids and immunosuppressive agents), as well as supplements.<sup>15</sup>

Despite the fact that there are several factors associated with a low serum vitamin D concentration, from the epidemiological point of view, vitamin D deficiency has been related to the presence and activity of autoimmune rheumatic diseases, as well as other chronic diseases, the major ones being cardiovascular diseases, hypertension and cancer.<sup>16</sup>

Thus, SLE patients not only show changes in bone metabolism; there are also alterations related to the immunological function of vitamin D through vitamin D receptor genes, major histocompatibility complex class II genes, microRNA, the renin-angiotensin-aldosterone system, apolipoprotein E, liver X receptor and Toll-like receptors. Vitamin D also exerts a protective influence on SLE patients, as it is a defense against the damage caused by ultraviolet light, metalloproteases, heme oxygenase-1, prostaglandins, cyclooxygenase-2 and oxidative stress.<sup>17</sup>

On the other hand, different studies in SLE patients show deficiency or insufficiency in the serum vitamin D concentrations, which are correlated with disease activity. There is also a correlation with the season of the year, cumulative glucocorticoids and serum creatinine concentration.<sup>18</sup> Similarly, there is evidence to support the notion of vitamin D deficiency as a possible risk factor for the development of SLE, and that supplementation with this vitamin could be useful for the prevention of SLE, or perhaps have a role in the treatment of SLE; even when added *in vitro*, vitamin D reverts several of the immunological abnormalities that characterize this disease.<sup>19</sup> Vitamin D supplementation is indicated in patients with SLE for the management of the changes related to bone mineral loss and, in the case of deficiency, can help to reduce the severity of the disease expression.<sup>20</sup>

Several vitamin D receptor gene polymorphisms have been reported and their relationship to lupus activity has been described.

<sup>☆</sup> Please cite this article as: García-Carrasco M, Romero JLG. Vitamina D y enfermedades autoinmunes reumáticas. Reumatol Clin. 2015;11:333–334.

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The variants associated with the onset of the disease are BsmI and FokI, which appear to be conditional upon chronic infections and low serum vitamin D concentrations.<sup>21</sup> Synthetic agonists of vitamin D receptor have antiproliferative, anti-inflammatory, immunomodulatory and antimicrobial properties. The use of these agonists will probably be an additional tool in the management of autoimmune diseases.<sup>22</sup>

With respect to RA, Cutolo et al. point out the changes in the serum vitamin D concentration and the increase in the severity of joint symptoms in patients with this disease. Specifically, they found that the lowest vitamin D concentration and the highest RA activity occur in winter. On the other hand, in susceptible populations, high vitamin D intake lowers the risk of developing RA and, in individuals who already have the disease, it reduces RA activity.<sup>23</sup> Another study in RA patients reports an inverse relationship between intake of high-dose vitamin D and disease activity, and the stimulation of regulatory T lymphocyte proliferation and self-reactive T lymphocyte apoptosis have even been observed.<sup>24</sup>

Other autoimmune diseases that have some relationship to vitamin D deficiency are Sjögren's syndrome,<sup>25,26</sup> Graves' disease,<sup>27</sup> Hashimoto's thyroiditis, T1D,<sup>28</sup> MS,<sup>29</sup> primary biliary cirrhosis<sup>30</sup> and myasthenia gravis.<sup>31,32</sup> Bellastella et al. found significantly lower serum vitamin D levels in the 3 types of autoimmune polyendocrine syndrome (type 1, T1D; type 2, Addison's disease + T1D; and type 3, autoimmune thyroid disease + T1D + another autoimmune disease), when compared with a control group, demonstrating a direct relationship between low levels of this vitamin and the presence of autoimmune disease.<sup>33</sup>

In conclusion: (1) vitamin D is a hormone with immunomodulatory properties that improves the innate immune response and induces self-tolerance in the acquired immune response; (2) there is epidemiological evidence suggesting that low vitamin D levels are related to the severity of several autoimmune diseases; (3) the dysfunction of the vitamin D receptor appears to be one of the molecular pathways associated with the increase in autoimmune diseases; and (4) there is limited evidence concerning vitamin D supplementation and autoimmune diseases; however, with the present studies, it is still difficult to understand the clinical utility of vitamin D, as well as its dosing and adequate treatment time.

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