Reumatol Clin. 2016;12(5):241–243

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

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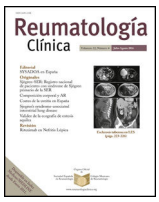

Editorial

Vitamin D and cardiovascular disease in patients with systemic lupus erythematosus☆

Vitamina D y enfermedades cardiovasculares en pacientes con lupus eritematoso sistémico

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Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology, in which genetic, environmental and immunological factors participate. It can affect joints, kidneys, skin, nervous system and cardiovascular system. The patients present a high risk of development of early cardiovascular disease, with atherosclerosis being the most frequent cardiac disease.[1–3] Manifestations like myocarditis, valve diseases, thrombosis, vasculitis and accelerated atherosclerosis have been identified.[4] In fact, we have reported that a large percentage of patients with SLE have structural or functional heart disease.[5] Cardiovascular risk factors have been extensively studied in SLE patients, in whom hypertension, dyslipidemia, tobacco use and diabetes mellitus do not explain the accelerated cardiovascular disease.[1,5] Therefore, it is important to considerate the so-called nontraditional factors or those related to the disease: disease duration, age at diagnosis, disease activity, corticosteroid doses and presence of antiphospholipid antibodies.[1,6] Among the unclassical risk factors for the development of atherosclerosis, vitamin D deficiency has been proposed in patients with SLE,[7,8] although a number of studies do not show this association.[9,10]

Vitamin D is a hormone with an immunoregulatory role that induces improvement in phagocytosis and reduces major histocompatibility complex class II DR in dendritic cells, while it induces maturity in natural killer cells and $CD4^+CD25^+FOXP3$ T cells, with the ability to mediate immune tolerance, reducing the development of autoimmune disorders.[11] These findings support different studies *in vitro*, in which the low serum vitamin D concentrations were related to the decrease in the expression of T helper (Th) 17 and Th1 proinflammatory cytokines and the increase in that of Th2 and T regulatory cytokines.[12–14] Some of these studies suggest that vitamin D supplementation could prevent endothelial damage produced by neutrophil extracellular traps,[15] in which there is a decrease in interferon α (IFNα) and inhibition of antigen-presenting cells.[16,17] Moreover, this vitamin can reduce interleukin (IL) 6 and IL-10 messenger RNA expression and increase that of transforming growth factor (TGF)-f3 and the percentage of T regulatory cells.[18] It has also been observed that vitamin D supplementation decreases the expression of Th1, Th17 and B cells, with reduction in the production of anti-DNA autoantibodies.[19,20]

There is controversy as to whether vitamin D deficiency actually contributes to the atherosclerosis in SLE patients, and if supplements with that vitamin can reduce cardiovascular risk in these patients. Our group has reported that patients with SLE have a high vitamin D insufficiency and deficiency with respect to the healthy population.[21] The deficiency of vitamin D is related to the absence of exposure to sunlight and the use of sunscreens as part of the treatment of photosensitivity of the patients with this disease, as is the history of chronic kidney disease and the use of chronic corticosteroids, anticonvulsants and antimalarial agents,[8,9] with lupus nephritis[22] and accumulated doses of corticosteroids[23,24] the most important factors.

The disease activity in SLE patients and its possible relationships with serum vitamin D level has also been controversial. Chen et al. demonstrated that vitamin D supplementation can modulate the production of proinflammatory cytokines and reduce the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score,[20] with each relationship between vitamin D and disease activity having been corroborated by other studies.[12,25,26] On the other hand, Sahebari et al. did not observe this corroboration.[23]

The administration of vitamin D supplementation can be useful in those individuals with cardiovascular risk factors, due to the fact that there is a possible association of the vitamin D deficiency and subclinical atherosclerosis.[27] The deficiency of this vitamin has been related to hyperlipidemia, insulin resistance, blood flow disturbances and arterial stiffness.[28,29] In SLE patients, there is a relationship of cardiovascular involvement with risk factors such as severe disease activity, collateral effects of immunosuppressant agents and obesity.[30] Moreover, diverse studies demonstrate that vitamin D deficiency is related to a greater expression of metabolic disorders and insulin resistance, but not to subclinical atherosclerosis or cardiovascular involvement in patients with SLE.[31,32]

☆ Please cite this article as: García-Carrasco M, Romero-Galvez JL. Vitamina D y enfermedades cardiovasculares en pacientes con lupus eritematoso sistémico. Reumatol Clin. 2016;12:241–243.

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With relationship to vitamin D supplements, concentrations of 4000 IU daily or 25,000 IU monthly do not reduce proinflammatory cytokines as does interferon γ,[33] disease activity or cardiovascular involvement in SLE patients. Other studies demonstrating that 300,000 IU in a bolus followed by 50,000 IU administered monthly during 1 year did not show marked modifications in disease activity.[34,35] However, these doses have an adequate safety margin, and achieve increases in T regulatory cells and decreases in the proinflammatory Th1 and Th17 immune responses.[36] Abou-Raya et al. demonstrated that patients with SLE and vitamin D deficiency had a decrease in proinflammatory cytokines and an increase in the hemostatic markers following supplementation.[37]

Although the doses and duration of vitamin D administration are not known, sustained doses to achieve a concentration of 32 ng/mL can improve the vascular blood flow and reduce apoptosis of the vascular[38] endothelium and neutrophil activity in SLE patients.[15] Lertratanakul et al. found a relationship between vitamin D deficiency with hypertension, hyperlipidemia and an increase in C-reactive protein; however, in this deficiency, they did not find an independent factor in the incidence of cardiovascular events. On the other hand, they did find an association between the serum vitamin D levels, with greater cardiovascular risk when analyzed with the successive concentration in the groups with greater serum vitamin D levels and, thus, with greater concentration when the cardiovascular risk was lesser.[39] Skaaby observed a relative risk of 0.95 for each 10 nmol/L higher in the vitamin D level for a decrease in triglycerides, hyperlipidemia and metabolic syndrome, but there was no relationship to the incidence of myocardial infarction or stroke.[40] Given the evidence of the association of vitamin D with cardiovascular risk in SLE patients, we can conclude a series of important points: (1) It is probable that vitamin D deficiency in patients with SLE is related to a greater disease activity; (2) The cardiovascular complications of SLE patients are related to the serious of the disease activity, the collateral effects of immunosuppressant agents and the standard cardiovascular risk factors; (3) The vitamin D deficiency in SLE patients seems to have more to do with metabolic disorders than with cardiovascular disease *per se*; (4) Maintaining optimal serum vitamin D levels in SLE patients would probably be a protector of cardiovascular risk; and (5) At the present time, it is reasonable to give supplemented vitamin D doses to any patient with deficiency of this vitamin and/or standard cardiovascular risk factors.

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