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Carta ao Editor

Vitamin D supplementation in patients with rheumatic diseases – the process of making a meta-analysis, its adversities and learnings

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Numerous epidemiologic studies have linked vitamin D to rheumatic diseases. For example, people living near the equator have a lower risk of developing autoimmune conditions, probably due to more vitamin D synthesis in their skin[1]. A recent study[2] illustrated this hypothesis by detecting a higher prevalence of autoantibodies and lower 25-OH vitamin D serum levels in a United States population when compared to a Sierra Leone population with the same genetic background. Furthermore, a seasonal variation in vitamin D synthesis by the skin has also been demonstrated, which may explain the seasonal increased risk of developing autoimmune diseases[3].

More recently, experimental studies began exploring new molecular actions of vitamin D, which could physiologically link it to rheumatic conditions[4]. Recent *in vitro* and *in vivo* studies have shown an important immune modulatory effect by vitamin D, which enhances innate immune activity[5] and regulatory T cells[6,7], while decreasing adaptive immune activity[8], mainly Th17 and Th9 lymphocytes[6,9,10], both involved in autoimmune disorders development[10-12].

Such findings could provide a pathobiological explanation as to why there is so much evidence linking vitamin D to rheumatic diseases prevalence and activity. However, still little is known about clinical effects of vitamin D supplementation in patients with rheumatic diseases[13].

Such conditions are very prevalent, affecting estimated 7 million Americans, 300 thousand of them being children[14], with potential to severe sequelae and mainly decreased quality of life[15,16]. For example, when Systemic Lupus Erythematosus is active, it may course with kidney failure, myocarditis and seizures, which can lead to death, but also compromise short and long-term functionality and quality of life. Rheumatoid Arthritis, on the other hand, poses less life-threatening complications, but is one of the most limiting rheumatologic diseases[17]. It is also important to stress that accessible specific therapeutic targeting molecular structures are not available[18].

Therefore, it would be interesting to verify if a simple, relatively cheap and safe therapy[19], as vitamin D supplementation, could provide promising clinical outcomes as Lupus activity reduction, or improvement in

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pain control for patients with Rheumatoid Arthritis.

In order to do this, randomized controlled trials that evaluated clinical and/or laboratorial outcomes after vitamin D supplementation in patients with rheumatic diseases were searched through five databases (MEDLINE, EMBASE, LILACS, COCHRANE, and CINAHL).

We concluded that the vast majority of studies is observational and still few randomized clinical trials evaluate clinical benefits of vitamin D supplementation; and the existing ones are not homogenous regarding intervention, length of supplementation, control groups and outcomes analyzed. Most of the studies also had a high risk of bias regarding a series of parameters.

Furthermore, some of them provided "pre-processed" data, instead of raw data, which made it impossible to compare to other studies and produce new numerical data, i.e., a meta-analysis.

Thus, the making of a systematic review and meta-analysis offers not only the knowledge about how to design and structure this kind of study, but it also matures the critical spirit regarding the design and data presentation of other types of studies, in order to contribute to the homogeneity of the knowledge, and to facilitate the compilation and comparison of statistical data. Furthermore, it can also help on preventing bias when designing a trial, which enhances its strength.

The objectives of this meta-analysis, then, were to provide a path to the making of novel clinical trials that could integrate the existing results and produce less biased and more robust evidence that corroborates our findings that vitamin D supplementation may decrease anti-dsDNA antibodies in Lupus and reduce Rheumatoid Arthritis recurrence.

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