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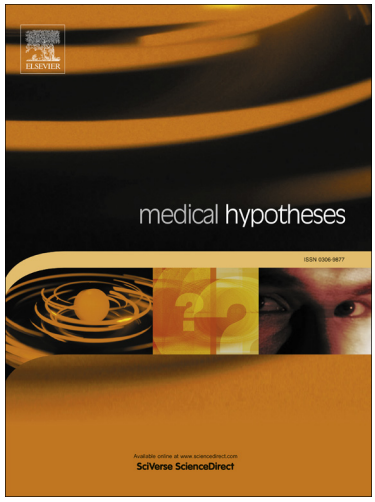


Vitamin D supplementation in multiple sclerosis-Can be done something more?

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# Vitamin D supplementation in multiple sclerosis-Can be done something more?

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To the Editor,

In a recently published article by Berezowska et al (1), they conclude that vitamin D supplementation may be a promising treatment for multiple sclerosis (MS), and represents a reliable background for further exploration of potential benefit regarding clinical improvements. Likewise, they add that a high dose vitamin D supplement intervention may contribute to bettering of physiological mechanisms, especially if baseline plasma levels are at the lower end of normal (1). Häusler and Weber (2) review the vitamin D potentially immune modulating mechanisms, followed by a summary of current and ongoing clinical trials, intended to assess whether vitamin D supplementation positively influences the outcome of central nervous system (CNS) demyelinating disease. However, in this article, it is underscored the fact that high doses of vitamin D could have negative effects in CNS demyelinating disease via T cell-stimulating effect of secondary hypercalcemia (2). Similar precautionary conclusions have been pointed out by other authors (1, 3-6). Although it has been described that following oral vitamin D supplementation, patients with MS have a lesser average increase in serum levels of 25-hydroxy-vitamin D (25-OH-D) than healthy individuals having similar starting concentrations (7), in MS patients vitamin D is usually administered in modest daily doses on the order of 1,000-3,000 IU in association with different disease-modifying therapies. This vitamin D supplementation is increasingly used, providing an added beneficial effect to patients (8).

Frequently, the vitamin D undesirable effects found by Fragoso et al. (9) in some MS patients treated with 8,000-150,000 IU/day (median 100,000 UI/day) are highlighted; nevertheless, these authors do not indicate what dosing procedure and clinical follow-up had been done in the patients included in this study, and what preventive measures had been taken to avoid the possible side effects of high doses of vitamin D. Other comments about the data and conclusions provided by Fragoso et al (9) can be seen in the paper of Kimball et al (10). Very possibly, the fear to a considered inevitable development of toxic effects, may explain the little attention awakened by some early studies, any published more tan eighty years ago (11, 12), on the posible treatment of autoimmune disorders, concretely rheumatoid arthritis, with massive doses of vitamin D.

Vitamin D is a powerful regulator of the immune system activity and, in accordance with the neurologist CG Coimbra from the University of Sao Paulo in Brazil, most patients with autoinmune diseases have an increased resistance to the immunomodulatory effects of vitamin D, mainly due to genetic polymorphisms, which requires the administration of massive doses of this prohormone to be clinically effective. It may be interesting to note here, that Henderson et al (13) have recently described the case of a woman with absence of circulating vitamin D-binding protein (VDBP), presenting a severe deficiency of vitamin D that did not respond to supplementation. This congenital deficiency of VDBP resulted in normocalcemia and mild disruption of bone metabolism, however, it was accompanied by a severe autoimmune disease (debilitating ankylosing spondylitis).

From years ago, the so-called “Coimbra protocol” with very high daily doses of vitamin D3 (initial dosage≈1,000 IU/kg of weight) has been used in America and Europe for the treatment of MS (more than 30,000 patients) and other autoimmune diseases. The clinical results seem

to be good, and the patients themselves treated by Coimbra in Sao Paulo, or by one of the doctors accredited to follow this protocol all over the world (14), recommend this therapeutic protocol with insistence and enthusiasm in their facebook groups (15) and in the books telling his own clinical history (16, 17). According to these patients, with MS and other autoinmune disorders, *"we constituted the best clinical trial for the Coimbra protocol validation".* Currently, some articles on this subject have been published (18, 19), and a recent study conducted in Brazil, shows that MS patients have a high degree of satisfaction with the vitamin D treatment, whether exclusive or complementary (20).

The Coimbra´s protocol for autoimmune diseases treatment has not just been recognized, but neither evaluated, in the academic media. It is argued that are necessary more studies to determine the suitable vitamin D dosage, and perform protocolized clinical follow-up, to avoid undesirable toxic effects as the hypercalcemia with all its posible physiopathological complications. Nevertheless, these issues seem to have been resolved by Coimbra itself. Briefly it may be noted that the daily doses of vitamin D are established and adjusted through the serum parathormone (PTH) levels, and not those of 25-OH-D. Likewise, the patients must follow a diet with calcium restriction, magnesium suplementation, and a daily intake of at least 2.5 liters of water, to maintain a urinary calcium concentration below 250 mg/L, for kidney stones and nephrocalcinosis prevention. Another factor of great importance for a good clinical evolution of the patients, is the maintenance of an adequate emotional control, which, depending on the degree of affectation, could be achieved in approximately 90-95% of cases. Periodically analytical controls of, at least, serum calcium, phosphorus, urea, creatinine, PTH, and 25-OH-D, and also calcium in 24-hour urine samples, are performed. The biochemical and clinical monitoring of patients treated with this protocol for years, shows that, although they present very high levels of serum 25-OH-D (frequently greater than 1,000 ng/mL), with very low PTH values around to the inferior reference limit, do not develop hypercalcemia, hypercalciuria, or other toxic effects due to the massive doses administered of vitamin D. More details on this protocol are available in one of the most prestigious online information sources about vitamin D (21).

Although some studies, such as that of Martinsen and Burian (22), are already underway in different European countries, from here, I invite all those involved in the research and/or treatment of MS and other autoimmune diseases, that, free from prejudices, find out about the true therapeutic possibilities of the Coimbra protocol. Then, we can answer to the question raised by Hawkes et al. (23), if for MS patients, vitamin D is "*caviar or a dog's dinner".*

Disclosure statement.
The autor reports no conflicts of interest

**References**


1) Berezowska M, Coe S, Dawes H. Effectiveness of vitamin D supplementation in the management of multiple sclerosis: A systematic review. Int J Molec Sci. 2019; 20: 1301
2) Haüsler D, Weber MS. Vitamin D supplementation in central nervous system demyelinating disease-Enough is enough. Int J Molec Sci. 2019; 20: 218
3) Goischke HK. Vitamin D supplementation as add-on therapy in multiple sclerosis-Balance between benefit and risk?: A comentary on Vitamin D supplementation in central nervous system demyelinating disease-Enough is enough. Int J Molec Sci 2019; 20: 1553.
4) Mclaughlin L, Clarke L, Khalilidehkordi E, Butzkueven H, Taylor B, Broadley SA. Vitamin D in the treatment of multiple sclerosis: A meta-analysis. J. Neurol. 2018; 265: 2893-2905.
5) Pierrot-Deseilligny C, Souberbielle JC. Vitamin D and multiple sclerosis: An update. Mult Scler Disord. 2017; 14: 35-45.
6) Zahoor I, Haq E. Vitamin D and multiple sclerosis: An update. In: Multiple Sclerosis: Perspectives in Treatment and Pathogenesis . Zagon IS, McLaughlin PJ (editors), Codon Publications, Brisbane. 2017: 71-85.
7) Bargava P, Steele SU, Waubant E, Revijaran NR, Marcus J, Dembele M, et al. Multiple sclerosis patiens have a diminished serologic response to vitamin D supplementation compared to healthy controls. Mult Scler 2016; 22: 753-60.
8) Linden J, Granasen G, Salzer J, Svenningsson A, Sundström P. Inflammatory activity and vitamin D levels in a MS population treated with rituximab. Mult Scler J Exp Transl Clin. 2019; 5: 1-10.
9) Fragoso YD, Adoni T, Damasceno A, de Albuquerque-Damasceno CA, Brito-Ferreira ML, Finkelzsteijn A, et al. Unfavorable outcomes during treatment of multiple sclerosis with high doses of vitamin D. J Neurol Sci. 2014; 346: 341-342.
10) Kimball S, Hanwell HE, Burton JM, Heaney RP, Holick MF, Hollis B, et al. Vitamin D supplementation in multiple sclerosis: Making a case for clarity. J Neurol Sci 2014; 347: 391-392.
11) Dreyer I, Reed CI. The treatment of arthritis with massive doses of vitamin D. Arch Phys Therap. 1935; 16: 537-40.
12) Brohult J, Jonson B. Effects of large doses of calciferol on patients with rheumatoid arthritis. Scand. J. Rheumatol. 1973; 2: 173-176.
13) Henderson CM, Fink SL, Bassyouni H, Argiropoulus B, Brown L, Laha TJ et al. Vitamin D-binding protein deficiency and homozygous deletion of the GC gene. New Engl J Med 2019; 380: 1150-57.
14) Coimbra Protocol Doctors (accessed March, 25, 2019): https://www.google.com/maps/d/u/0/viewer?ll=42.16108947061385%2C13.05220517481689&z=5&fbclid=IwAR0R3GFly-tU90-WEeL5PiUI1vxSZId9zPVzTobYduilES7AFjH_hgn6vTo&mid=1fATZJUEhOsYYJdBY41h48FBkLaQ
15) Coimbra Protocol Facebook Groups (accessed March, 25, 2019): https://m.facebook.com/notes/o-tratamento-com-vitamina-d-do-dr-c%C3%ADcero-coimbra-portugal/grupos-e-p%C3%A1ginas-relacionados-com-o-protocolo-do-dr-c%C3%ADcero-coimbra/1722518301305431/
16) Domene AC. Multiple Sclerosis and (lots) Vitamin D: My eight-year treatment with the Coimbra protocol for autoinmune diseases. CreateSpace Independent Publishing Plattform, 2016.
17) Butler J. Stop Multiple Sclerosis & Autoimmune Disease with High Dose Vitamin D: The first US patient treated by the first US Coimbra protocol doctor tells her story. Independently Published, 2017.
18) Finamor DC, Sinigaglia-Coimbra R, Neves LCM, Gutierrez M, Silva JJ, Torres LD et al. A pilot study assessing the effect of prolonged administration of highly doses of vitamin D on the clinical course of vitíligo and psoriasis. Dermato-Endocrinol. 2013; 5: 222-234.
19) Cadegiani FA. Remission of severe miastenia gravis after massive-dose of vitamin D. Am J Case Rep. 2016; 17: 51-54.

20) Alves-Reis CF, Pereira-Guimarâes F. Multiple sclerosis patients perception about the use of vitamin D in clinical therapy. Rev Bras Cienc da Vida. 2017; 5 (1): 1-19.
21) GrassrootsHealth (accessed March, 25, 2019): https://grassrootshealth.net/blog/dr-coimbras-protocol-multiple-sclerosis/
22) Martinsen I, Burian N. Adherence to the Coimbra Protocol in Adults with Autoimmune Disease. Bachelor Thesis, University College Copenhagen. 2019 (accesed March, 25, 2019): https://docs.google.com/document/d/1e4RWjjdGJfM8bgBpU_9ua9RydSxA1QZxGTwzZX8N5lc/edit?fbclid=IwAR0QAE3mNEszfA0GcF3YOGsHFBTXaKZxzAX2k5gqw3CB9pqS1uMCATrU2OE
23) Hawkes C, Giovannoni G, Lechner-Scott J, Levy M, Waubant E. Multiple sclerosis and vitamin D. Caviar or a dog's dinner?. Mult Scler Relat Disord. 2019, 28, A1-A2.