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Could Metabolomics Clarify the Multiple Sclerosis – Vitamin D Metabolites Relationship?

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It has been accepted for more than 30 years that multiple sclerosis (MS) is determined by a combination of genetic and environmental factors. Among the latter, Epstein–Barr virus infection, cigarette smoking and concentration of vitamin D are the most remarkable [1,2]. The deficiency of vitamin D as a risk factor for multiple sclerosis (MS) was proposed, in principle, to explain a latitude gradient in MS prevalence that correlates with ultraviolet radiation duration and intensity as the main source of vitamin D in most populations [3]. More than 30 years later and after huge amounts of research and publications on the vitamin D–MS relationship the opinion of scientists working in this field is that further work is needed to determine the optimal vitamin D dose for MS prevention or treatment [4-8]. When high doses of vitamin D have been used the treatment has never proved effective or safe. Attracted by the option of a "natural" and "curative" treatment for MS, even neurological or systemic complications were observed while high doses of vitamin D were being used [9,10].

Treatments with vitamin D and/or their metabolites have involved mainly vitamin D3 [9,10], but also treatments with vitamin D3 and with vitamin D2 have been compared [4]); treatment with the prehormone 25-hydroxyvitamin D [9,10], or with the thousand times less abundant biologically active metabolite 1,25-dihydroxyvitamin D has been widely reported. Measurements of both the mono- and dihydroxy metabolites as response to treatment metabolites have been scant [4-8,11,12]. Most times, the methods for measurement of both have been RIA or ELISA, which have been or have not been assessed by testing programs, and only sporadically a method based on liquid chromatography with mass spectrometry detection has been the choice for determination, despite it is considered the gold method for vitamin D metabolites [13,14]. This last type of methods also allow measurement of other metabolites such as the 24,25-dihydroxyvitamin D metabolite or even the isomeric forms of the circulating metabolite 25-hydroxyvitamin D; information that could help in MS studies [15].

The relationship between vitamin D and genetic MS risk factors has been widely studied and the achievements discussed in recent reviews [16,17]. Thus, the genes encoding the enzymes that convert 25-hydroxyvitamin D into the dihydroxy metabolites in position 1 or 24 (1-α-hydroxylase or 24-hydroxylase, respectively) and their variants [18-22]; the vitamin D receptor (VDR) and its polymorphisms [23-25]; and the VDR binding sites present in the DNA that can affect transcription of the corresponding genes have been all the subject of in depth research [16]. Despite the studies on the relationship of vitamin D and/or its metabolites with genetic MS risk factors last since more than 30 years, the controversial results clearly shows that the planned research have not been the appropriate.

Taking into account that at least two hydroxymetabolites of vitamin D are involved in this old and controversial research, metabolomics seems to be the most suited discipline to go into the problem in a different way through the support offered by:

(i) The present methods based on mass spectrometry for the determination of the two forms of vitamin D (vitamins D_3 and D_2) and a number of their metabolites (*viz.*, 25-hydroxyvitamin D_3 epimers, 25-hydroxyvitamin D_2, 1, 25-dihydroxyvitamin D_3, 1, 25-dihydroxyvitamin D_2 and 24, 25-dihydroxyvitamin D_3) at the very low levels some of them exist in blood, even at "insufficiency" or "deficiency" status [25].

(ii) The growing development of metabolomics, the well-known pathways of vitamin D metabolism and the enzymes involved in them.

The present state of methods for determination of vitamin D metabolites and metabolomics could give response to questions such as:

1. Does the ratio of 25-hydroxy vitamin D epimers have some influence on the effect of this metabolite on MS?
2. How the formation of the dihydroxy metabolites [1,24,25] influences the effects of vitamin D on MS?
3. Is the ratio between the two dihydroxy metabolites an influential factor on their behavior and effects on MS?
4. What type of proteomics information and its relationship with MS can provide the relative concentration of the two dihydroxymetabolites through the relative activity of 1-hydroxylase and 24-hydroxylase?
5. Could the relative activity of 1-hydroxylase and 24-hydroxylase provide up-stream information on transcritomics and genomics, as happened in other up-stream metabolomics studies [26,27].

Response to the previous questions would provide enough data either to recommend or not recommend oral vitamin D supplementation for MS primary prevention and to establish differentiation between vitamin D and non-vitamin D sun exposure effects, which are not clear at present [28]. From this knowledgement, new lines of action could be addressed.

References

1. Ascherio A, Munger KL (2007) Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol 61: 288-299.
2. Ascherio A, Munger KL (2007) Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. Ann Neurol 61: 504-513.
3. Goldberg P (1974) Multiple sclerosis: vitamin D and calcium as environmental determinants of prevalence (a viewpoint) Part 1: Sunlight, dietary factors and epidemiology. Int J Environ Stud 6: 19-27.
4. Holick MF, Chen TC (2008) Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 87: 1080S-6S.
5. Smolders J, Peelen E, Thewissen M, Menheere P, Tervaert JW, et al. (2009) The relevance of vitamin D receptor gene polymorphisms for vitamin D research in multiple sclerosis. Autoimmun Rev 8: 621-626.

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6. Ascherio A, Munger KL, Simon KC (2010) Vitamin D and multiple sclerosis. Lancet Neurol 9: 599-612.

7. Simon KC, Munger KL, Ascherio A (2012) Vitamin D and multiple sclerosis: epidemiology, immunology, and genetics. Curr Opin Neurol 25: 246-251.

8. Sundström P, Salzer J (2015) Vitamin D and multiple sclerosisâ€"from epidemiology to prevention. Acta Neurol Scand 132: 56-61.

9. Fragoso YD, Adoni T, Damasceno A, de Albuquerque Damasceno CA, et al. (2014) Unfavorable outcomes during treatment of multiple sclerosis with high doses of vitamin D. J Neurol Sci 346: 341-342.

10. Toghianifar N, Ashtari F, Zarkesh-Esfahani SH, Mansourian M (2015) Effect of high dose vitamin D intake on interleukin-17 levels in multiple sclerosis: A randomized, double-blind, placebo-controlled clinical trial. J Neuroimmun 285: 125-128.

11. Cantorna MT, Hayes CE, DeLuca HF (1996) 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. Proc Natl Acad Sci U S A 93: 7861-7864.

12. Correale J, Ysrraelit MC, Gaitán MI (2009) Immunomodulatory effects of Vitamin D in multiple sclerosis. Brain 132: 1146-1160.

13. Yamout B, Karaky NM, Mahfouz RA, Jaber F, Estaitieh N, et al. (2016) Vitamin D receptor biochemical and genetic profiling and HLA-class II genotyping among Lebanese with multiple sclerosis - A pilot study. J Neuroimmunol 293: 59-64.

14. Mena-Bravo A, Ferreiro-Vera C, Priego-Capote F, Maestro MA, Mouriño A, et al. (2015) Quantitative analytical method to evaluate the metabolism of vitamin D. Clin Chim Acta 442: 6-12.

15. Lutsey PL, Eckfeldt JH, Ogagarue ER (2015) The 25-hydroxyvitamin D3 C-3 epimer: distribution, correlated, and reclassification of 25-hydroxyvitamin D status in the population-based atherosclerosis risk in communities study (ARIC). Clin Chim Acta 442:75-81.

16. Lin R, Charlesworth J, van der Mei I, Taylor BV (2012) The genetics of multiple sclerosis. Pract Neurol 12: 279-288.

17. Kalman B, Toldy E (2014) Genomic binding sites and biological effects of the vitamin D--VDR complex in multiple sclerosis [corrected]. Neuromolecular Med 16: 265-279.

18. Orton SM, Morris AP, Herrera BM, Ramagopalan SV, Lincoln MR, et al. (2008) Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis. Am J Clin Nutr 88: 441-447.

19. Ramagopalan SV, Dyment DA, Cader MZ, Morrison KM, Disanto G, et al. (2011) Rare variants in the CYP27B1 gene are associated with multiple sclerosis. Ann Neurol 70: 881-886.

20. Ban M, Caillier S, Mero IL, Myhr KM, Celius EG, et al. (2013) No evidence of association between mutant alleles of the CYP27B1 gene and multiple sclerosis. Ann Neurol 73: 430-432.

21. Sawcer S, Hellenthal G, Pirinen M, Spencer CC (2011) Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 476: 214-219.

22. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, et al. (2010) Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet 376: 180-188.

23. Tajouri L, Ovcaric M, Curtain R, Johnson MP, Griffiths LR, et al. (2005) Variation in the vitamin D receptor gene is associated with multiple sclerosis in an Australian population. J Neurogenet 19: 25-38.

24. Cox MB, Ban M, Bowden NA, Baker A, Scott RJ, et al. (2012) Potential association of vitamin D receptor polymorphism Taq1 with multiple sclerosis. Mult Scler 18: 16-22.

25. Mena-Bravo A, Priego-Capote F, Luque de Castro MD. Two-dimensional liquid chromatography coupled to tandem mass spectrometry for vitamin D metabolite profiling including the C3-epimer-25-monohydroxyvitamin D3. J Chromatogr A, in press.

26. García-Alcalde F, García-López F, Dopazo J, Conesa A (2011) Paintomics: a web based tool for the joint visualization of transcriptomics and metabolomics data. Bioinformatics 27: 137-139.

27. Kuo TC, Tian TF, Tseng YJ (2013) 3Omics: a web-based systems biology tool for analysis, integration and visualization of human transcriptomic, proteomic and metabolomic data. BMC Syst Biol 7: 64.

28. Jalkanen A, Kauko T, Turpeinen U, Hämäläinen E, Airas L (2015) Multiple sclerosis and vitamin D during pregnancy and lactation. Acta Neurol Scand 131: 64-67.

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