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 D3 and D2) and a number of their metabolites (viz., 25-hydroxyvitamin D3 epimers, 25-hydroxyvitamin D3, 1, 25-dihydroxyvitamin D3, 1, 25-dihydroxyvitamin D2 and 24, 25-dihydroxyvitamin D3) 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 knowledge, new lines of action could be addressed.

References


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