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Vitamin D and multiple sclerosis. Prevalence of hypovitaminosis D

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Summary

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system whose etiology is unknown. Certain environmental factors, such as vitamin D, may have an influence on its pathogenesis, although the optimum threshold for vitamin D necessary to maximise its extraosseous benefits is not known. This article reviews, non-systematically, studies world-wide which relate vitamin D with MS. Overall, there are no significant differences between cases of MS and controls. In the case series, hypovitaminosis D with respect to values considered to be normal is seen in patients with MS, an observation which may also apply to healthy individuals. To be able to clarify the extent of the relationship between vitamin D and MS, further prospective studies are needed.

Key words: *vitamin D, multiple sclerosis, epidemiology, prevalence, deficit.*

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) triggered by an inflammatory disorder which causes focussed infiltrations of lymphocytes into the brain and spinal cord, causing demyelination and axonal damage over time[1]. Although we are able to establish a diagnosis of MS, its aetiology remains unknown. It appears that certain environmental factors may contribute to a susceptibility to this disease, without any one of them alone being sufficient to trigger it. Among those factors proposed are the geographical latitude of residence before puberty, which is associated with exposure to sun, and blood levels of vitamin D[2]. 1,25-dihydroxy-vitamin D ($1,25(OH)_2D_3$) is the form responsible for most, but not all, of the biological actions of vitamin D, while 25-hydroxy-vitamin D ($25(OH)D_3$) is the form most common in the blood[3], which is why it is this metabolite which is determined in most studies of vitamin D.

The importance of vitamin D for muscular-skeletal health and bone metabolism is widely known[4-7]. With reference to this, the optimum level of $25(OH)D_3$ in the blood has been established as being between 32-50 nM/L (12.8-20 ng/ml), this being the level associated with the maximum suppression of PTH[8]. According to the Institute of Medicine (IOM) of the United States, the recommendations regarding blood levels of vitamin D are that: values of $25(OH)D_3$ <30 nM/L are deficient; those between 30-50 nM/L may be insufficient for some people; and levels >50 nM/L are sufficient for nearly the whole population[9]. However, it is not completely clear what are the optimum levels necessary in relation to the extraosseous effect of vitamin D.

The prevalence of MS and its north-south gradient in the northern hemisphere is inversely correlated with exposure to UVB ultraviolet light[10]. However, this latitudinal gradient has been attenuated in the last 25 years, which suggests that environmental factors may play a determining role, exposure to sun and vitamin D being potential candidates which may explain this phenomenon.

This is because an inverse relationship between levels of vitamin D and the risk of developing MS has been observed, as well as which changes in lifestyle associated with lower exposure to sun and, therefore, less synthesis of vitamin D, may contribute to the attenuation of the latitudinal gradient[11].

The significance of vitamin D in relation to solar exposure dependent on the latitude of residence is due to the immunomodulatory properties attributed to vitamin D. The activated T & B lymphocytes have nuclear receptors specific to vitamin D, so that this vitamin increases the differentiation of the monocytes to macrophages and reduces the proliferation of activated lymphocytes, the synthesis of IgG by the B cells, the generation and activation of natural killer cells and the expression of various inflammatory cytokines, such as TNF-α, IL-1, IL-6 and IL-8[12].

In this article a non-systematic review is carried out of the literature to evaluate the prevalence of hypovitaminosis D in patients with MS in different regions across the world (Table 1), in search of a common pattern which could help us form a hypothesis for new lines of clinical research in this field.

Prevalence of hypovitaminosis in multiple sclerosis

Hypovitaminosis D is a phenomenon prevalent in southern Europe, the Middle East, India, China and Japan, on which the skin-type, sex, type of clothing usually worn, nutrition, the use of vitamin complexes, the body mass index and degree of urbanisation all have an influence[13]. These zones correspond according to latitudinal gradient with areas of average prevalence for MS, except the north of Europe, which would be a zone of high prevalence[14]. So, the question is, to what extent is hypovitaminosis D associated with MS as a causal factor, as a consequence, or simply an incidental finding which leads us to erroneous associations with this phenomenon.

Europe

In Europe, various studies have been carried out which have tried to determine the influence of blood levels of vitamin D on MS. Data taken from a transverse case-control study in Finland published in 2005[15] show that there are no differences in blood levels of $25(OH)D_3$ between the groups in the study, with average values of 50 nM/L for patients with MS and 57 nM/L for the controls. When the data is segmented according to whether the samples were taken during winter or summer months, there continues to be no statistically significant differences in the winter months (41 nM/L for MS and 44 nM/L for the controls), but the values were significantly lower in those patients with MS in the summer months (58 nM/L in MS vs 85 nM/L in the controls). A detail to be taken into account in this study is that the patients in the control group were not completely healthy, but that 65% were neurological patients without MS, but with diagnoses of Bell's palsy, hemiplegic migraine, migraine with aura, post-lumbar-puncture cephalgia, paraesthesia, paroxysmal positional vertigo, dizziness, central scotoma, extrapyramidal syndrome, depression, epileptic crisis and fibromyalgia. In addition, in Finland in 2008 another case-control study was published[16] with healthy controls drawn from laboratory staff, matched according to age, sex and place of residence. In this study it was observed that the seasonal variations in blood levels of vitamin D were the same for the patients with MS as for the healthy subjects. The average values obtained were 57.6±20.5 nM/L for those with MS and 55.3±22.4 nM/L for the healthy controls. Establishing a cut-off point of ≤37 nM/L, 43% of the patients with MS and 53% of the controls had a deficit of $25(OH)D_3$, while, if the cut-off point was set at 50 nM/L only 17% of the patients with MS and 22% of the controls had insufficient levels of vitamin D. Also in Finland, due to its high prevalence of MS, a study has

recently been published which studied blood levels of 25(OH)D_3 during pregnancy, and after, in patients with MS in comparison with healthy controls[17]. This study revealed that the patients with MS had lower levels of 25(OH)D_3 during the whole of the pregnancy compared with the healthy controls, with a striking decrease occurring in the first month post-partum. The authors described how this decrease was statistically significant in the group of patients with MS whose levels moved from 46.9 nM/L in the third trimester of pregnancy to 36.5 nM/L in the first month post-partum, and that 73% of the patients with MS had a vitamin D deficit, defined as <50 nM/L, during pregnancy. This was postulated to be related to a possible interaction between vitamin D metabolism and the hormonal state of these patients.

In Sweden, another Nordic country with a high prevalence of MS, a case-control study was published in 2012, subdivided into two groups, one consisting of patients with MS, matched 2:1 with their controls, and the other group consisting of pregnant patients matched 5:1 with their controls[18]. The results produced by this study show that the average blood levels of 25(OH)D_3 were similar between cases and controls, both in the subgroup of pregnant subjects (39 nM/L in the cases and 40 nM/L in the controls) and in the non-pregnant subgroup 40 nM/L in the cases and 39 nM/L in the controls). The study also confirmed the presence of seasonal variations, such that levels >75 nM/L were four times more frequent in the summer than in the winter.

There are authors who suggest that for hypovitaminosis D to have a real influence on the development of MS it needs to be present before the onset of the disease, meaning that if normal levels of vitamin D are maintained in the early stages of life, the risk of MS is reduced. For this reason, in 2014 a study was published, also carried out in Sweden, which tried to establish the risk of suffering MS according to the vitamin D status in the new born[19]. It was carried out in a cohort of all new born babies born in Sweden since 1975 and compared data from 459 cases and 663 controls at birth and of 298 cases and 307 controls at the start of the disease. The results obtained were that the vitamin D status at birth was not associated with the risk of MS in a wide section of the population of a city with moderate levels of sun. The values of 25(OH)D_3 at birth were 29.4 nM/L in the cases and 29.9 nM/L in the controls, at the point of diagnosis with MS, the blood levels were 65.0 nM/L for the cases and 67.8 nM/L for the controls, data which do not support the idea proposed to date of the role of vitamin D in the aetiology of MS.

In the Netherlands, the data available in relation to levels of 25(OH)D_3 in patients with MS are those from a prospective longitudinal study of 73 patients with relapsing-remitting MS published in 2012[20]. The average value of 25(OH)D_3 in this case series is 69 nM//L with a coefficient of variation of 41%. As in other similar articles, the seasonal variation in values of vitamin D follows a sinusoidal curve, and concludes that levels of 25(OH)D_3 <50 nM/L are associated with a 1.9 times higher risk of an exacerbation of the disease in an interval of 4 weeks compared with patients with levels >50 nM/L.

In Ireland, three cities are described with different prevalence for MS, which, from highest to lowest are: Donegal, Wexford and South Dublin. In 2011 a study was published regarding the prevalence of MS in Ireland, looking for an association between MS and vitamin D or genotype HLA[21]. The average value of 25(OH)D_3 was 38.6 nM/L in the cases and 36.4 nM/L in the controls, with no statistically significant difference. What was striking was that the levels of vitamin D were significantly higher in South Dublin (50.7 nM/L), which has the lowest prevalence of MS in Ireland, than in the two other cities (36.9 nM/L in Donegal and 39.7 in Wexford).

To demonstrate the possible involvement of vitamin D in patients with MS resident in Paris, a multicentre regional case-control study was carried out during the first quarter of 2010[22] which revealed lower levels of vitamin D in those affected by MS than in the control group, these being 14.5 nM/L and 16.7 nM/L, respectively. In another study carried out between June 2008 and February 2009[23] it was reported that 83% of the patients had insufficient vitamin D, defined as levels of 25(OH)D_3 <75 nM/L, and that 17% had a deficit of 25(OH)D_3, with an average value of 52 nM/L.

In terms of Spain, the data available to date are from a case-control study carried out in Cataluña which was published in 2012[24]. In this study, seasonal variations in blood levels of vitamin D were also reported, such that in the summer no statistically significant differences were found between the groups studied, but in the winter the results confirmed that the patients with relapsing-remitting multiple sclerosis (RRMS) had levels of 25(OH)D_3 lower than that of the controls (16.6 nM/L and 24.1 nM/L, respectively). However, this was not the case in patients with primary progressive multiple sclerosis (PPMS). These findings are simplified by the authors who conclude that in winter 65% of the patients with RRMS had insufficient levels of 25(OH)D_3 (<20 nM/L) in comparison with 45% of the healthy controls.

America

In America, the contribution made in 2006[25] by Munger et al. in relation to levels of 25(OH)D_3 and the risk of MS is notable. This was a case-control study carried out in seven million US military personnel, of whom 257 became cases of MS, and who were subsequently compared with two controls for each case of the same age, sex, race and date of taking the blood sample. It was observed that the average levels of 25(OH)D_3 were 75.2 nM/L in the white population, 29.7 nM/L higher than in the black population in which the average value was 45.5 nM/L, and 8.6nM/L higher than in the Hispanic population and other ethnic groups which had an average level of 66.6 nM/L. The study concluded that among white people the risk of developing MS

is reduced by 41% for each 50 nM/L increase in the level of $25(OH)D_3$, with no statistically significant differences between the sexes. In addition, it was observed that there was 51% less risk of MS among patients who had levels of $25(OH)D_3$ equal to or greater than 100 nM/L in comparison with those who had levels lower than 75 nM/L.

In New York a study was carried out and published in 1994[26] in which it was concluded that there was a high prevalence of vitamin D deficit and a reduction in bone mass in patients with MS. This study was carried out in 80 women with MS who were admitted to a tertiary hospital, without their being matched with healthy controls. The average blood levels of $25(OH)D_3$ in 52 samples obtained from this population was 42.9 nM/L without there being seasonal variations.

In California, another study on vitamin D and MS compared the blood levels in white patients with that of Hispanic patients, all of whom had already been diagnosed with MS, without healthy controls. This transverse study published in 2012[27] showed that the average levels of $25(OH)D_3$ were 32.1 nM/L among the Hispanic patients and 24.6 nM/L among the white patients, and that these levels did not experience seasonal fluctuations in the Hispanic population.

At the time of conducting this review regarding vitamin D in patients with MS there were no data from South America published in PubMed. Even in a publication by Brum in 2104[28] it is stated that there are no comparative studies on blood levels of vitamin D in Brazil's regions, although there had been studies in other selected risk groups such as postmenopausal women without MS[29].

Asia

We take as an example of the prevalence of hypovitaminosis D in Asia a study carried out in India published in 2013[30] which obtained average values for $25(OH)D_3$ of 39.0 nM/L in those patients with MS, significantly lower than the healthy controls who had levels of 45.5 nM/L. If only those patients who were in clinical remission (without exacerbations) were studied these levels would increase to 46.0 nM/L, while in those patients with exacerbations it was 37.0 nM/L.

Oceania

A study was carried out in Australia, published in 2011, whose aim was to evaluate whether exposure to sun and the state of vitamin D in the blood measured as $25(OH)D_3$ were associated with developing a first demyelinating event[31]. This was a multicentre case-control study with patients in four Australian cities: Brisbane, Newcastle, Geelong and the western district of Victoria, and in the island of Tasmania. For those patients who had had their first demyelinating event the average levels of vitamin D were 75.1.nM/L, and for the controls, 80.4 nM/L.

Another case-control study carried out in Tasmania and published in 2007[32] concludes that the average values of vitamin D were similar between the two groups studied, being 51.4 nM/L for the cases and 53.1 nM/L for the controls.

Prevalence of hypovitaminosis D beyond multiple sclerosis

Up to this point we have discussed how blood levels of vitamin D may have an influence on the overall increase in the epidemiology of MS due to its association with exposure to sun according to the latitudinal gradient. However, it is suggested that environmental factors such as lifestyle or dietary habits may be modifying factors which influence the prevalence of hypovitaminosis D across the globe.

The main source of vitamin D for most people is exposure to sun and the phototype of the skin, since the pigmentation related to melanin allows each person's skin to have sufficient vitamin D to satisfy their requirements. However, international recommendations which have been made in relation to exposure to sun to prevent skin cancer (avoiding exposure to the sun, clothing which leaves little skin exposed to the sun, sun protection…) has resulted in a world population at risk of hypovitaminosis D[33].

Reduced blood levels of $25(OH)D_3$ have been associated with other diseases apart from MS, such as cancer, cardiovascular disease, other autoimmune rheumatic diseases[3] and even with autism and cephalgia[34], as well as in the healthy population.

It is notable how populations which we previously assumed to be without vitamin D deficiency and healthy, may come to have low blood levels of 25-OH-vitamin D. This situation has been reported amongst medical students, researchers in health sciences and resident doctors due to their long working days without exposure to sun[35-38], as well as amongst inhabitants of urban areas which allow little access to sunlight[39]. But it is even more unlikely to find that individuals who appear to have adequate exposure to sun may also have reached reduced levels of $25(OH)D_3$, with average values of 32 ng/ml (80 nM/L), as is the case with surfers[40]. In any case, there are populations which, due to sociocultural or religious factors, have a high prevalence of hypovitaminosis D, such as has been reported in regions of Turkey and Morocco relating the clothing worn, this deficiency being higher among women[41], above all if the veil is worn, possibly dropping as low as 3.6 ng/ml (9 nM/L) in Turkey[42].

The importance of these findings is reinforced when we see that the blood levels of vitamin D are related to cardiovascular health[43-46], such that higher levels of $25(OH)D_3$ are associated with a reduction in the risk of cardiovascular disease, diabetes, metabolic syndrome and arterial hypertension, as well as in the risk of death, be it of cardiovascular origin, cancer[47,48] or due to other causes[49].

In the same way that vitamin D deficiency is considered to be an immunomodulatory factor in multiple sclerosis, as we reported at the start of this article, this effect has also been reported in other rheumatic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, lupus or Behçet's disease[50-54], in intestinal inflammatory disease and in coeliac disease[55-57].

Table 1. Levels of 25(OH)D_3 in patients with multiple sclerosis in different countries of the world

Author	Year	Country/ City	Sample size	25-OH-D_3 (nM/L)	25-OH-D_3 (ng/ml)	p value	Reference
Soilu-Hanninen	2005	Finland	40 cases / 40 controls	50 cases / 57 controls	20 / 22.8	0.202	(15)
Soilu-Hanninen	2008	Finland	23 cases / 23 controls	57.6 cases / 55.3 controls	23.0 / 22.1	0.81	(16)
Jalkanen	2015	Finland	15 cases 6 controls	46.9 antepartum - 36.5 postpartum 62.7 antepartum - 52.8 postpartum	18.8 - 14.6 25.1 - 21.1	0.02 0.54	(17)
Salzer	2012	Sweden	37 cases pregnancy (control 5: 1) 102 cases no pregnancy (control 2: 1)	40 cases - 39 controls 39 cases - 40 controls	16 - 14.4 14.4 - 16	0.99 0.97	(18)
Ueda	2014	Sweden	459 cases 663 controls	Neonates: 29.4 cases - controls 29.9 Debut: 65.0 cases - controls 67.8	11.8 - 12.0 26 - 27.1	>0.05	(19)
Runia	2012	Netherlands	73 cases	69	27.6	<0.05	(20)
Lonergan	2011	Ireland	632 cases / 632 controls	38.57 / 36.41	15.4 - 14.6	>0.05	(21)
Neau	2011	France	170 cases / 170 controls	14.5 cases / 16.7 controls	5.8 - 6.7		(22)
Pierrot-Deseilligny	2009	France	167 cases	52	20.8		(23)
Grau López	2012	Spain	40 cases RRMS 15 cases PPMS 40 controls	16.6 24.1 22.1	6.6 9.6 8.8	0.0001 0.7	(24)
Munger	2006	United States	148 caucasian cases 296 white checks 109 black / hispanic cases 218 black / hispanic controls	75.2 white 45.5 black 66.6 hispanic	30.2 18.2 26.6	0.001	(25)
Nieves	1994	New York	80 cases	42.9	17.2		(26)
Amezcua	2012	California	80 hispanic cases 80 caucasian cases	80.2 61.5	32.1 24.6	0.001	(27)
Pandit	2013	India	110 cases (63 outbreaks) 108 controls	39 46.5	15.6 18.6	0.003	(30)
Lucas	2011	Australia	216 cases / 395 controls	75.1 cases / 80.4 controls	30.0 / 32.2	>0.05	(31)
van der Mei	2007	Tasmania	136 cases / 272 controls	51.4 cases / 53.1 controls	20.6 / 21.2	>0.05	(32)

RRMS: relapsing-remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis.

Conclusions

Vitamin D as an environmental factor influencing the pathogeny of MS is an increasingly accepted hypothesis in view of the existing evidence in this respect but, although its role in bone mineral metabolism is indisputable, it is still not completely clear what the threshold for vitamin D should be considered optimum to achieve its extraosseous benefits, among which is its immunomodulatory effect. On conducting this review to understand the state of hypovitaminosis D in the population with MS across the world we see that, overall, there are no statically significant differences between cases and controls[15,16,18,21,24,31,32]. One point to take into account is the correct choice of controls. For example, in a study by Soilu et al.[15], healthy controls were not selected, but controls unaffected by MS, and in the study by Nieves et al.[26] the cases were drawn from hospitalised patients, which means we already start with a series of cases with a higher degree of clinical affectation or other types of bias resulting from the hospitalisation itself.

In those studies in which only cases affected by MS were studied[20,23,26,27] the focus was on hypovitaminosis D with respect to the values considered normal for the general population, which are usually 20 ng/ml or 50 nM/L, but by not having healthy controls with which to compare them, it is not possible to attribute this observation to the disease itself, since we do not know if there are other factors involved such as lifestyle habits or clothing worn.

A study which concluded that there was hypovitaminosis D attributable to MS is that of Jalkenen et al.[17], which compared the situation pre- and post-partum in patients affected by MS and which observed how in the first month post-partum the drop in blood levels of vitamin D is clearly greater in the cases. The study by Pandit el al.[30] also showed that those patients with MS had lower levels of vitamin D than the controls, but it should be noted that approximately half of the cases were in clinical relapse at the time the sample was taken for the determination of vitamin D, which could mean a confusion factor since when only the subgroup without relapse was studied the average values of $25(OH)D_3$ were similar to that of the control group.

It appears that the clinical form of the disease influences the levels of vitamin D, as is described in the study by Grau-López et al.[24], which revealed that the primarily progressive forms had higher hypovitaminosis D than the relapsing-remitting forms, but only in the summer months. Another factor which seems to influence the prevalence of hypovitaminosis D in patients with MS, as described in the article by Munger et al.[25], is the patient's race, such that levels of $25(OH)D_3$ are higher in white people, followed by Hispanic people, with black people having the lowest levels.

What is still not clear after all this discussion is when is the right moment to avoid this hypovitaminosis. The study by Ueda et al.[19] is revealing with respect to this question. While the other studies discussed refer to a determination of a cross section, the Ueda study refers to a prospective cohort, in which those patients with blood levels of vitamin D lower at birth are those who subsequently most commonly develop MS. This observation reaffirms the importance of supplementing vitamin D in pregnant women as a measure of primary prevention, not only in MS but in as many other pathological situations where vitamin D has been seen to be involved. Thus we come to the dilemma – is hypovitaminosis a predisposing factor for MS, or is it a consequence of the disease? – since by being incapacitated they are less exposed to sun, and their fatigability increases with exposure to sun.

Taking into account the fact that most of the studies do not demonstrate differences between the cases and the controls, and that hypovitaminosis D exists in healthy individuals[35-42], could it be the case that vitamin D has an immunomodulatory effect only in individuals with a predisposition of suffering a particular disease? So, it seems that new, well-designed prospective studies will be needed in order to be able to glimpse in the future the extent and scope of the extraosseous effects of vitamin D.

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