Journal of Photochemistry and Photobiology B: Biology xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology B: Biology

journal homepage: www.elsevier.com/locate/jphotobiol

The role of vitamin D in multiple sclerosis

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ARTICLE INFO

Article history:
Received 3 November 2009
Received in revised form 12 February 2010
Accepted 1 April 2010
Available online xxxx

Keywords:
Multiple sclerosis
Vitamin D
UV-radiation
Diet
25(OH)D
Genes
Sex differences
EAE
Latitude
Immunopathogenesis

ABSTRACT

Multiple sclerosis (MS) risk is determined by environmental influences acting on the individual genetic background. Recent epidemiologic and experimental evidence supports a role of low environmental supplies of vitamin D in mediating an increased susceptibility to MS.

We review available evidence suggesting that vitamin D status may influence MS risk and even modulate clinical disease activity. The level of serum 25-hydroxyvitamin D providing these effects remains to be determined.

1. Multiple sclerosis pathogenesis

Multiple sclerosis (MS) is a chronic disease of the central nervous system, affecting young adults, with a female predominance. The course is usually relapsing-remitting for about 10 years, followed by a secondary progressive phase. The pathogenic mechanisms have not been fully elucidated. Histology shows T helper cell type 1-mediated chronic inflammation, demyelination, and axonal degeneration [1].

MS risk is determined by as yet incompletely defined genetic and environmental factors. The window of exposure to environmental factors covers a period of many years, possibly starting even before conception, due to epigenetic influences. Genetic epidemiologic studies strongly indicate that environmental factors act at a broad population level, rather than in the familial microenvironment [2].

2. The UV-radiation/vitamin D hypothesis for MS risk

One of the most striking features of MS is its geographic distribution, showing, with some notable exceptions, a pattern of high MS frequency in areas where sunlight exposure is low and, consequently, opportunity for vitamin D synthesis in the skin is limited [3–7]. A meta-analysis has shown that measured values of 25-hydroxyvitamin D (25(OH)D) decreased with latitude in Caucasians, but not in non-Caucasians [8].

As early as 1960, Acheson proposed a relationship between the geographic distribution of MS, exposure to sunlight, and vitamin D metabolism [9]. In 1974, Goldberg hypothesised further that MS-prone individuals have particularly high vitamin D requirements because of genetic defects, and that "in geographical regions of abundant vitamin D the greater vitamin supplies (...) would offset the inborn metabolic defects" [10,11]. Hayes, Cantorna, and DeLuca presented a unifying UV-radiation/vitamin D hypothesis in 1997, supported by data from animal experiments [12].

The only prospective data so far showed that circulating levels of 25(OH) vitamin D $\geqslant$ 100 nmol/L were associated with a lower risk of MS in whites [13].

For comprehensive reviews of the evidence supporting a role of UV-radiation (UVR) and vitamin D in the pathogenesis of MS, the reader is referred to recent publications [7,14,15].

2.1. UV-radiation

Newer data have challenged the concept of increasing prevalence of MS with increasing latitude in both hemispheres [16]. However, MS prevalence in Australia and in France could be closely

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doi:10.1016/j.jphotobiol.2010.04.003

Please cite this article in press as: M.T. Kampman, L.H. Steffensen, The role of vitamin D in multiple sclerosis, J. Photochem. Photobiol. B: Biol. (2010), doi:10.1016/j.jphotobiol.2010.04.003

predicted by regional UVR levels [4,6], and a recently published geospatial analysis confirmed a strong association between UVR and MS distribution [17]. Ecological studies have shown an inverse correlation of sunlight exposure through outdoor activities during the period spanning from childhood to adolescence, but also into adulthood, with MS risk [18–21], even north of the Arctic Circle [22]. It has even been hypothesised that vitamin D status during pregnancy is a factor mediating the maternal parent of origin effect in MS susceptibility [23]: vitamin D insufficiency during winter pregnancies might explain the excess of MS in those born in May in Europe and Canada [24–27].

Possible pathways for immunosuppressive effects of UVR exposure in immune-mediated disorders that are likely to be independent of vitamin D synthesis are also recognised [17,28].

2.2. Dietary vitamin D

The effect of dietary vitamin D on MS risk has been less studied. Swank and co-workers reported a strong correlation of high animal fat and butter intake with the high incidence of MS in the inland and dairy areas of Norway in 1952, but they did not consider a protective effect of the high fish diet in the low incidence coastal fishing districts [29]. Most humans are not dependent on dietary vitamin D supplies [30], and a correlation of vitamin D from food with 25(OH)D is only found when UVR exposure is low [31–33]. In the Nurses' Health Study cohort following 187,000 women aged 25–55 years at inclusion, total vitamin D intake and use of vitamin D supplements $\geqslant$ 400 IU/day, but not vitamin D intake from food, were associated with higher serum 25(OH)D levels and lower MS risk [34]. In a MS case-control study in Norway north of the Arctic Circle, we found that use of cod-liver oil supplements when growing up was associated with less MS in the subgroup of respondents with low summer outdoor activities [22].

2.3. Genetic background

Reports on novel gene-environment interactions continue to increase our understanding of the role of vitamin D in MS. Convincing evidence has been published that vitamin D regulates a gene in the HLA class II-region, the vitamin D response element, that is consistently expressed in homozygous carriers of the MS associated HLA-DRB1*1501 allele [35]. This hypothesis is strengthened by a study finding an association between the presence of the HLA-DRB1*15 risk allele and season of birth in persons with MS, but not unaffected siblings or controls [27]. In this context, it is interesting that the HLA-DRB1*15 genotype was maternally transmitted three times more often than it was paternally transmitted. This type of parent of origin effect is generally thought to be a result of genomic imprinting through epigenetic modifications of the genome [36,37]. Conversely, a significant genetic influence on regulation of circulating 25(OH)D concentrations has been found in MS twins [38].

The contribution of VDR gene polymorphisms to immune regulation in MS is not fully understood [39]. It has been reported from Tasmania that a functional variant of the vitamin D receptor (VDR), the Cdx-2 genotype, interacts with sun exposure in childhood to influence MS risk [40], implying that vulnerability to poor vitamin D status may be determined by genetic variations. However, in a French study concluded that season of birth but not VDR receptor promoter polymorphisms (among which Cdx-2) was a risk factor for MS [41]. First studies have been performed to assess the role of vitamin D binding protein [42–44]. The modification of the association of past sun exposure with MS risk by "red hair colour" genotype provides further support for a causal effect of UVR/vitamin D in the aetiology of MS [45]. Interestingly, three patients with vitamin D-dependent rickets have been described who all developed MS [46].

2.4. Sex differences

The disproportional increase in the incidence of MS in women, that was first observed in Canada, is likely to be caused by sex-specific exposure or susceptibility to environmental factors [47]. Data supporting an interaction between female sex, possibly mediated by oestrogen, and vitamin D in MS risk are accumulating. A protective effect of sun exposure was only observed in female monozygotic twins [48], and the association of sun sensitive skin types with disability was only found in untreated female MS patients [49]. Also the association between the "red hair colour" variant genotype and MS was more evident for women [45]. In Norway north of the Arctic Circle, summer outdoor activities in childhood and adolescence decreased MS risk. In subgroup analysis (adjusted for cod-liver oil and fish intake), this association was significant in women (73 cases), but not in men (38 cases) [5], though the number of men in the study might be insufficient to detect an association.

In vitro studies of MBP (myelin basic protein)-specific T cell proliferation have shown sex differences in the metabolism of vitamin D that were confirmed by treating male MBP-specific T cells with 17β-estradiol in the assay [50].

2.5. Animal studies

Animal studies of the experimental allergic encephalomyelitis (EAE) model of MS have shown that EAE could be prevented by whole-body UV irradiation and that vitamin D hormone completely inhibited EAE induction and progression [14]. Sex differences in vitamin D metabolism were first reported in the EAE model: A cholecalciferol containing diet inhibited severe EAE only in female mice, indicating a sex difference in vitamin D metabolism in the CNS [51]. The same group showed recently that 17β-estradiol is essential for VDR gene expression and function in the inflamed CNS in EAE mice [52].

3. Vitamin D in the immunopathogenesis of MS

A role of vitamin D in the immunopathogenesis of MS is biologically plausible. Vitamin D is a potent immune modulator [53,54], and a role for vitamin D has also been proposed in other immune-mediated diseases, a.o. diabetes type I, rheumatoid arthritis, and inflammatory bowel disease [54].

Direct genomic signalling by active hormonal vitamin D ($1,25(OH)_2$ D3) occurs through the vitamin D receptor (VDR), which is present in multiple cells of the immune system as well as in neurons and glial cells in the human brain [14,55]. Activation of the VDR by hormonal vitamin D stimulates a shift from proinflammatory Th1 responses to anti-inflammatory Th2 responses [14]. Proliferation assays show an association of high 25(OH)D levels with an improved regulatory T cell function in persons with MS [56,57].

EBV infection appears to be a necessary (but not sufficient) condition for adult MS to develop [58]. Holmøy was the first to propose that poor vitamin D status modulates the immune response to EBV in a way that increases the risk of developing MS [59–61].

4. Vitamin D sufficiency

Vitamin D status, measured as serum concentration of 25(OH)D, reflects a combination of cutaneous vitamin D synthesis under the influence of UV-B light and oral ingestion of vitamin D.

Most humans depend on sun exposure (UV-B radiation) to satisfy their requirements for vitamin D. UV-B exposure depends on geographic factors like latitude and altitude, atmospheric

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components such as ozone, cloud cover, and suspended particles (pollution) [62] as well as on individual variations in time spent outdoors, skin pigmentation, covering by clothes, sunbathing habits and sunscreen use, but also age, sex, fat mass, and genes [8,38,63,64].Useful increases in vitamin D status can be achieved by UV-B doses small enough to produce only minimal tanning [65]. A 10–15 min whole-body exposure to peak summer sun can produce vitamin D equivalent to 10,000–20,000 IU in white adults [30]. Even north of the Arctic Circle, UV-B exposure contributes significantly to serum 25(OH)D levels [5,31,66]. People with coloured skin living at high latitudes may have to increase their dietary vitamin D intake to compensate for reduced dermal vitamin D production [8]. Inuit, a population with limited opportunity for cutaneous vitamin D synthesis, appear to have an enhanced renal conversion of 25(OH)D to $1,25(OH)_2D$, thus improving the utilisation of available 25(OH)D [67].

The only foods that naturally contain a considerable amount of vitamin D, fatty seafood, egg yolks, and chanterelle mushrooms, provide substantial amounts of vitamin D only in a minority of people. More important sources of ingested vitamin D are fortified foods, cod-liver oil, and vitamin supplements [5].

Biochemically, hypovitaminosis D can be defined as a serum level of 25(OH)D at which serum parathyroid hormone starts to increase. Based on this fact, current expert opinion defines vitamin D sufficiency as 25(OH)D levels $\geqslant$ 75 nmol/L. Levels between 50 and 74 nmol/L reflect marginal vitamin D status, and values less than 50 nmol/L vitamin D deficiency [68,69]. Levels around 100 nmol/L or more may be required for optimal immune function and bone mineral density [13,70,71]. In a pilot study, even higher serum levels of 25(OH)D (mean 413 nmol/L, range 66–729 nmol/L) were found to be beneficial and safe in persons with MS [72].

Increasing numbers of people may need to take vitamin D supplements to ensure vitamin D sufficiency as sun exposure is being discouraged by health authorities and traditional diets containing vitamin D are being abandoned [67]. Supplementation with a weekly dose of about 20,000 IU cholecalciferol can be expected to result in approximately 50 nmol/L increase of 25(OH)D [30,73]. It has to be kept in mind, though, that it is not clear whether all potential benefits can be provided by oral supplementation with vitamin D [28].

5. Vitamin D status in persons with MS

Data on vitamin D status in persons with MS are not available for large unselected groups. Associations of 25(OH)D with a.o. disability, body mass index, and sex, limit comparability of results. Measurements from different centres are influenced by regional variations in the general population, whereas differences in assay type probably are a minor concern [8]. Studies retrieved by searching PubMed are compiled in Table 1.

Levels of 25(OH)D have also been measured in cerebrospinal fluid (CSF). Holmøy et al. did not find significant differences between CSF 25(OH)D in 36 persons with relapsing-remitting MS compared with persons with other inflammatory or non-inflammatory neurological diseases [82].

6. Vitamin D status and UV exposure in relation to MS clinical activity

6.1. Observational studies

Some studies suggest a relationship between low serum vitamin D levels and disease activity in relapsing-remitting MS but the causality of this relationship has not been proven.

Table 1
Vitamin D status in persons with MS and controls.

	25(OH)D nmol/L (n)		*P*-value	Type of controls
	Patients	Controls		
Tasmania [32]	51 (136)	53 (272)	n.s.	Matched
Canada [38]	76 (83)	75 (83)	n.s.	Unaffected twins
Argentina [56]				
RRMS	47 (92)	61 (60)	$P < 0.001$	Not matched
PPMS	52 (40)		n.s.	
Finland [63,13]				
Summer	58 (40)	85 (40)	$P = 0.023$	Not matched
Winter	50 (40)	57 (40)	n.s.	
Finland [56]	58 (23)	55 (23)	n.s.	Not matched
Netherlands[74]				
Summer	97 (103)	103 (110)	n.s.	Not matched
Winter	60 (103)	66 (110)	n.s.	
Turkey [75]	43 (31)	108 (30)	$P < 0.001$	Not matched
UK [76]	69 (29)	67 (22)	n.s.	Not matched
US [77]	40 (54)	67 (49)	n.d.	Not matched
Canada [73]				
Spring	78 (12)	–		
France [78]	52 (167)	–		
Netherlands [79]	63 (267)	–		
Norway [80]				
Winter	59 (80)	–		
US [81]	43 (52)			
Caucasians [8]	–	68 (96 studies)		

25(OH)D: mean value of group studied; n.s.: not significant; n.d.: not determined.

Lower vitamin D levels have been reported during relapses than remission in relapsing-remitting MS patients [56,83,84]. Serum levels of 25(OH)D were associated with both relapse rate [79,85] and disability [32,79] in MS patients. The significant correlation between winter serum 25(OH)D levels and EDSS in a heterogeneous sample of Dutch MS patients, was restricted to women [74].

A recent report showed that children with higher serum 25(OH)D concentrations at presentation with an acquired demyelinating syndrome had a lower risk of early MS diagnosis [86].

Brain magnetic resonance imaging (MRI) parameters are commonly used as surrogate markers for MS disease activity. In patients with relapsing-remitting MS, no correlation was found between serum 25(OH)D and MRI parameters [84]. In another cross-sectional study, neither serum nor CSF vitamin D status was associated with inflammatory disease activity [82].

More indirectly, variations in relapse rate, markers of inflammation, and number of brain lesions on magnetic resonance images (MRI) have, with few exceptions, shown a seasonal pattern that can be related to variation in UVR exposure and vitamin D status [85,87–91].

6.2. Intervention studies

In pilot studies, treatment with vitamin D compounds reduced both relapse rate [72,85,92,93] and disability progression [72,93]. First results from a 96 week trial of 20,000 IU (500 μg) cholecalciferol a week (or placebo) and 500 mg calcium a day in our Department will become available in 2010 (ClinicalTrials.gov NCT00785473).

Effect of vitamin D supplementation on surrogate markers of disease activity has also been reported. Supplementation with 1000 IU cholecalciferol increased serum levels of the anti-inflammatory cytokine transforming growth factor (TGF)-β1 [94]. In a 28 week safety study of increasing daily doses of vitamin D (4000–40,000 IU cholecalciferol), the overall number of MRI lesions decreased significantly from baseline to the end of the trial [73].

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7. Vitamin D for prevention and treatment of MS?

The evidence reviewed in this paper provides indications that vitamin D sufficiency reduces MS risk. To date, no study has convincingly shown a therapeutic effect of vitamin D compounds on MS.

More studies are needed to determine the optimal levels of vitamin D that result in immunological and clinical benefits to patients with MS.

Adequately powered placebo-controlled trials will be required to assess the efficacy of high-dose vitamin D supplementation in patients with MS and patients with a "clinically isolated syndrome" suggestive of a first MS attack.

Only a large randomised trial can answer the question whether vitamin D supplementation in the general population can contribute to preventing MS and other more prevalent immune-mediated disorders, e.g. diabetes type I, rheumatoid arthritis, and inflammatory bowel disease. Sex differences in vitamin D metabolism suggest that women may benefit more from the immunomodulatory effect of vitamin D than men.

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Please cite this article in press as: M.T. Kampman, L.H. Steffensen, The role of vitamin D in multiple sclerosis, J. Photochem. Photobiol. B: Biol. (2010), doi:10.1016/j.jphotobiol.2010.04.003