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Review

Multiple sclerosis, osteoporosis, and vitamin D

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ABSTRACT

Multiple sclerosis (MS) is associated with reduced bone mass and higher frequency of osteoporosis. Although high-dose short-term intravenous glucocorticoid regimens cause a decrease in bone formation, this effect is usually reversible and osteoporosis in MS patients may be independent of the short-term corticosteroid treatment. Clinical evidence suggests an important role of vitamin D as a modifiable risk factor in MS. Low circulating levels of vitamin D have been found in MS patients, especially during relapses, suggesting that vitamin D could be involved in the regulation of the clinical disease activity. Vitamin D mediates its function through a single vitamin D receptor (VDR). Polymorphisms of the VDR have major effects on vitamin D function and metabolism, and some VDR genotypes have been linked to osteoporosis and MS. Because the safety of high doses of vitamin D has not been established yet, vitamin D hasn't been used in enough doses to increase the serum level to a desired therapeutic target. Future clinical trials should determine the upper limit of vitamin D intake in order to achieve therapeutic benefit in MS patients.

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1. Introduction

Multiple sclerosis (MS) is associated with reduced bone mass and vitamin D deficiency (Table 1). The underlying pathophysiology of the bone disease may be due to acute and long-term glucocorticoid use, progressive immobilization, vitamin D deficiency, and possibly skeletal muscle atrophy [1].

Bone mass density and vitamin D are reduced in patients with MS in comparison to healthy age- and sex-matched controls [2]. Because of their lower bone mass, MS patients have more frequent fractures than do their healthy age- and gender-matched peers [3]. Injurious falls among middle aged and older adults with MS were reported in 50% of patients [4]. A study in long-term care residents with MS demonstrated that these patients were at high risk for fracture [5]. Vitamin D repletion in MS patients who are deficient might reduce, to some extent, the rate of bone loss and decrease osteoporosis-related fractures [6,7].

The low bone mass in MS patients seems to involve both sexes. Thus, a study in 80 female patients in comparison to a healthy reference population showed that BMD was significantly reduced, probably secondary to vitamin D deficiency and induced hyperparathyroidism [6]. Similarly, evaluation of 40 male MS patients (mean age 51.2 years) revealed reduced BMD in 80% of patients (42.5% with osteopenia and 37.5% with osteoporosis). Among them, 21% had vertebral, rib or extremities fractures. Multivariate linear regression

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Table 1
Bone mineral density and MS.

	Patients	Bone mineral density	Other findings	Authors' conclusion
Formica et al, 1997 [1]	71 cases 71 controls	Reduced total body bone mineral content only in non- ambulatory MS patients (8%, -0.3 +/- 0.1 SD, P<0.04)	Reduced fat free mass only in non- ambulatory MS patients (5%, -0.3 +/- 0.1 SD, P<0.01)	Physical disuse was the main cause for the reduction in bone mass Glucocorticoid treatment was the major cause of the reduction in fat-free mass
Ozgocmen et al, 2005 [2]	31 cases 30 controls	MS patients had significantly lower BMD at the lumbar spine and femur trochanter	EDSS scores in the patients were inversely correlated with proximal femur BMD but not with spinal BMD	Ambulatory status was the main cause of low BMD in MS
Cosman et al, 1998 [3]	54 cases 49 controls	Bone fractures in 22% of patients and 2% of controls Reduced BMD in MS patients Reduced vitamin D in MS patients	Duration of steroid treatment beyond 5 months and ambulatory status were both predictors of bone loss	MS patients have more frequent fractures and lose bone mass more rapidly than do their healthy age- and gender-matched peers, in part related to insufficient vitamin D
Nieves et al, 1994 [6]	80 female cases	BMD was 1 to 2 SDs lower in MS women compared with a healthy reference population.	BMD were lowest when 25(OH)D levels were deficient	Vitamin D deficiency is prevalent in MS and is probably a significant cause of low BMD
Weinstock-Guttman et al, 2004 [7]	40 male cases	80% of patients had a reduced bone mass	21% had vertebral, rib or extremities fractures	Association between MS and pathological bone loss

MS: Multiple sclerosis; BMD: Bone mineral density; EDSS: Expanded disability status scale; SD: Standard deviation.

analysis indicated that the EDSS and BMI were the important factors associated with low BMD at the femoral neck. No clear association between intravenous steroid therapy and BMD was evident in the multivariate analysis [7].

The effect of immunomodulatory therapies has also been tested in MS patients. A study that evaluated the effect of interferon-beta on BMD in 30 females and 18 males with MS found that males but not females treated with interferon-beta exhibit a decrease in BMD, a paradoxical effect since interferon-beta inhibits the development of osteoclasts, the cells responsible for bone resorption [8]. However, another study in 37 patients showed that immunomodulatory therapy (interferon beta-1a in 70%, interferon beta-1b in 27% and glatiramer in 3%) had a favourable effect on bone in patients with MS even in the presence of pulse steroid therapy [9].

2. Steroids

The effects of steroid treatment that MS patients frequently receive during disease exacerbations have been studied extensively. High-dose, short-term intravenous glucocorticoid regimens cause an immediate and persistent decrease in bone formation and a rapid and transient increase of bone resorption. Discontinuation of such regimens is followed by a high bone turnover phase and overall no change in bone mineral density 6 months after therapy [12]. Repeated pulses of methylprednisolone did not result in substantially increased risk of subsequent osteoporosis in MS patients [10].

In physically active patients with MS treated with low-dose steroids, the bone-turnover markers were not different from controls [11]. The change in femoral density in poorly ambulatory patients may have been related to inactivity rather than the steroid pulse [12]. Duration of steroid treatment beyond 5 months and poor ambulatory status were both predictors of bone loss [3]. Thus, presence of osteoporosis in MS patients may be independent of short-term corticosteroid treatment [13,14].

3. MS pathogenesis and vitamin D

MS pathogenesis seems to involve both genetic susceptibility and environmental risk factors (vitamin D deficiency and Epstein-Barr viral infection) [15–19]. However, no cohesive explanation yet exists as to how environmental factors interact to induce a neurodegenerative autoimmune response. Summer outdoor activities in childhood and adolescence are associated with a reduced risk of MS and supplemental cod-liver oil may be protective when sun exposure is less, suggesting that both climate and diet may interact to influence MS risk at a population level [20]. Insufficient sunlight exposure and chronic viral infections have been proposed as unrelated environmental risk factors for MS. One important beneficial effect of solar ultraviolet light is its contribution to the cutaneous synthesis of vitamin D, a crucial hormone for bone health and its protective effects on the development of rickets, osteomalacia, osteoporosis, multiple sclerosis and several cancers [21–29]. After hydroxylation in the liver into 25-hydroxyvitamin D (25(OH)D) and kidney into 1,25-dihydroxyvitamin D (1,25(OH)2D), it can bind to the vitamin D-receptor mediating various processes [30]. Various cells involved in immune responses such as macrophages, dendritic cells, T cells and B cells, express the vitamin D receptor (VDR), and can both produce and respond to 1,25(OH)(2)D(3). Experimental evidence indicates that the 1alpha,25-(OH)2D3 may augment the function of suppressor T cells that maintain self tolerance to organ-specific self antigens [31], and may be beneficial for Th1-mediated autoimmune disorders such as MS [32,33]. Thus, vitamin D supplementation may help prevent the development of MS and may be a useful addition to therapy [34–39].

4. In vitro and animal studies

MS is a CD4+ T cell-mediated autoimmune disease and Th1 cells driven by IL-12 may be pathogenic T cells in human MS and EAE. Vitamin D3 and 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) inhibited induction of experimental autoimmune encephalomyelitis (EAE), in mice [40]. Several observations have shown that vitamin D inhibits proinflammatory processes by suppressing the enhanced activity of immune cells and may be beneficial for Th1-mediated autoimmune processes [32,33]. Treatment of activated T cells with 1,25(OH)2D3 also inhibited the IL-12-induced tyrosine phosphorylation of JAK2, TYK2, STAT3, and STAT4 in association with a decrease in T cell proliferation in vitro [41]. In addition, recent data indicated that IL-17-producing CD4+ T cells, driven by IL-23 and referred to as Th17 cells, play a crucial role in the pathogenesis of EAE [42].

Sequence analysis localised a single MHC vitamin D response element (VDRE) to the promoter region of HLA-DRB1 which is conserved in MS HLA-DRB1 homozygotes but not conserved in non-MS-associated haplotypes. Thus, expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D [43].

CD8(+) T cells were not necessary for 1 alpha,25-dihydroxyvitamin D(3) to suppress experimental autoimmune encephalomyelitis in mice [44]. Vitamin D(3) and 1,25-(OH)(2)D(3) strongly inhibited myelin oligodendrocyte peptide (MOG(35-55))-induced EAE in C57BL/6 mice, but completely failed to inhibit EAE in mice with a disrupted IL-10 or IL-10R gene. Thus, a functional IL-10-IL-10R pathway was essential for 1,25-(OH)(2)D(3) to inhibit EAE [45]. These results suggested that a genetic IL-10-IL-10R pathway defect could interact with an environmental risk factor, vitamin D(3) insufficiency, to increase MS risk and

severity [45]. Gene expression analysis suggests that 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by stimulating inflammatory cell apoptosis [46].

The 1,25(OH)(2)D(3) analog, TX527 (19-nor-14,20-bisepi-23-yne-1,25(OH)(2)D(3)), has a potent immunomodulatory and but a minimal calcemic effects in vivo. Addition of TX527 to IFN-beta resulted in additive immunomodulatory effects in experimental EAE prevention suggesting possible clinical benefit that should be tested in MS trials [47].

5. Vitamin D receptor

The genotypic associations support a role for the VDR gene to modulate the risk of developing MS (Table 2). Polymorphisms of the VDR have major effects on vitamin D function and metabolism, and should therefore be assessed in studies on vitamin D and MS [48].

An association of some VDR genotypes with osteoporosis and MS has been reported [49,50]. Three polymorphisms within the VDR gene were genotyped in 136 MS cases and 235 controls, and associations with MS and past sun exposure were examined by logistic regression. No significant univariate associations between the polymorphisms, rs11574010 (Cdx-2A>G), rs10735810 (Fok1T>C), or rs731236 (Taq1C>T) and MS risk were observed. However, a significant interaction was observed between winter sun exposure during childhood, genotype at rs11574010, and MS risk (P=0.012), with the [G] allele conferring an increased risk of MS in the low sun exposure group (</=2 h/day). No significant interactions were observed for either rs10735810 or rs731236, after stratification by sun exposure. These data provided support for the involvement of the VDR gene in determining MS risk, an interaction likely to be dependent on past sun exposure [51].

In addition to MS risk, vitamin D receptor gene polymorphisms may be related to the degree of disability in MS. In 512 patients with MS of at least 10 years duration, study of outcome or disability with the association of VDR single nucleotide polymorphisms (A/G(1229), C/G (3444), G/A(3944), CC(20965), CC(30056), F/f(30875), C/T(48200), T/t (65013)), showed that ff (30875) frequency was lower in cases with EDSS>or=6.0 than with scores<6.0 [52].

A study in 419 cases and 422 controls reported reduced risk of MS with the Fok I VDR ff polymorphism [53]. In the contrary, genotyping of 212 MS patients and 289 healthy controls for the Fok I VDR gene polymorphism and measurement of the vitamin D metabolites 25(OH)D and 1,25(OH)(2)D, showed no association of the Fok I VDR gene polymorphism with MS. However, the [F] allele was associated with lower winter and summer serum 25(OH)D levels in MS patients, and with lower 25(OH)D levels in healthy controls. Carriers of the [F] allele had higher 1,25(OH)(2)D/ 25(OH)D-ratios compared to their [f] allele counterparts [54]. Bsm I and Apa I polymorphisms of the VDR gene assessed from the DNA of 77 MS patients and 95 healthy controls, showed that the AA genotype and the [A] allele were significantly more prevalent in MS patients than in controls, suggesting increased risk [55].

The relatioship between red hair color variant genotype (MC1R Arg151Cys, Arg160Trp, or Asp294His alleles) and MS is complex suggesting that the melanocortin 1 receptor (MC1R) genotype may be causally related to MS risk [56]. A study described that the MC1R His294-encoding alleles was associated with increased MS risk and MC1R Glu84/Glu84 was linked with disability [53].

6. The vitamin D binding protein (DBP)

The DBP is the major plasma carrier protein of vitamin D and exerts several other important biological functions such as fatty acid transport, macrophage activation and chemotaxis. DBP is a highly polymorphic serum protein with three common alleles (Gc1F, Gc1S and Gc2) and more than 120 rare variants [57]. A study of two polymorphisms (codon 416 and codon 420) in the DBP gene through a case-control study involving 107 Japanese patients with MS and 109 healthy controls showed none of these polymorphisms to have an association with the occurrence of MS [58]. However, studies of DBP levels in CSF of patients with MS by proteomics analysis showed a correlation between the level of DBP and MS suggesting that DBP may be a potential useful biomarker for diagnosis or a medicine target for treatment of MS [59].

7. Clinical trials

Evidence from clinical studies on MS (Table 3) suggests an important role of vitamin D as a modifiable environmental factor in MS [60]. High circulating levels of vitamin D were associated with a lower risk of multiple sclerosis [61,62], especially if the 25-hydroxyvitamin D levels were measured before the age of 20 years [63]. Measurement of plasma

Table 2
VDR polymorphisms and MS.

	Patients	VDR polymorphisms examined	Result	Comment
Tajouri et al, 2005 [79]	104 cases 104 controls	Apa I, Taq I and Fok I restriction polymorphisms	Taq I [T] allele and Apa I [A] allele more prevalent in MS patients than in controls	Involvement of the VDR gene in MS risk
Dickinson et al, 2009 [51]	136 cases 235 controls	rs11574010 (Cdx-2 A>G) rs10735810 (Fok I T>C) rs731236 (Taq I C>T)	Increased MS risk with [G] allele of rs11574010 and reduced winter sun exposure in childhood (P=0.012)	Involvement of the VDR gene in MS risk
Fukazawa et al, 1999 [50]	77 cases 95 controls	Bsm1 endonuclease restriction polymorphism	Overexpression of the b allele (92.9 vs. 84.2%: P=0.0138) and homozygote bb (85.7 vs. 71.6%; P=0.0263) in MS patients	Association of MS risk with VDR gene polymorphism
Mamutse et al, 2008 [52]	512 cases	A/G (1229) C/G (3444) G/A (3944) CC (20965) CC (30056) F/f (30875) C/T (48200) T/t (65013)	F/f (30875) frequency was lower in cases with EDSS>or=6.0 than with scores<6.0 (OR=0.38, 95% CI=0.20-0.70)	Association of MS disability with VDR gene polymorphism
Partridge et al, 2004 [53]	419 cases 422 controls	Taq I and Fok I restriction polymorphisms	VDR ff (Fok I) was associated with reduced frequency in MS (OR=0.59)	Association of MS risk with VDR gene polymorphism
Niino et al, 2000 [55]	77 cases 95 controls	Bsm I and Apa I endonuclease restriction polymorphisms	Apa I AA genotype and the [A] allele more prevalent in MS patients than in controls	Association of MS risk with VDR gene polymorphisms
Smolders et al, 2009 [54]	212 cases 289 controls	Fok I (rs10735810)	No association of the Fok I VDR gene polymorphism with MS Both MS and controls carriers of the [F] allele had higher 1,25(OH)(2)D/ 25(OH)D-ratios	Association of Fok-I VDR gene polymorphism with vitamin D metabolism

MS: Multiple sclerosis; VDR: Vitamin D receptor; EDSS: Expanded disability status scale.

Table 3
Clinical trials of vitamin D in MS patients.

	Patients	Other parameters	Vitamin D	MS risk	Statistics/ Comments
Munger et al, 2006 [63]	257 cases 514 controls			In whites, MS risk decreased with increased vitamin D levels No association in blacks and Hispanics	OR: 0.59; 95% CI, 0.36-0.97 Inverse relationship of vitamin D with MS risk
Kragt et al, 2009 [80]	103 cases 110 controls	Inverse correlation of EDSS and vitamin D levels	Higher levels in summer	In women for every 10 nmol/L increase of serum 25(OH)D level the odds of MS was reduced by 19%	OR: 0.81; 95% CI, 0.69-0.95 Inverse relationship of vitamin D with MS risk and disability
Barnes et al, 2007 [64]	29 cases 22 controls		Higher levels in women than men with MS	No differences between cases and controls	Sex differences of vitamin D levels in MS patients
Correale et al, 2009 [65]	132 cases; 58 RRMS in remission; 34 RRMS in relapse; 40 PPMS 60 controls		Lower levels in relapse than remission	Lower levels in RRMS than controls No differences between PPMS and controls	Inverse relationship of vitamin D with RRMS risk and activity
Soilu-Hanninen et al, 2008 [71]	23 cases 23 controls	PTH higher in relapse than remission	Lower levels in relapse than remission	Vitamin D deficiency (S-25(OH)D < or = 37 nmol/l) in 50% of patients and controls	Inverse relationship of vitamin D with MS activity
Tremlett et al, 2008 [69]	199 cases	Positive association of URT infections and relapse	Lower levels in relapse than remission		Inverse relationship of vitamin D with MS activity
Van der Mei et al, 2007 [70]	136 cases 272 controls		Inverse correlation of EDSS and vitamin D levels	High prevalence of vitamin D insufficiency in both MS cases and controls	Inverse relationship of vitamin D with MS disability
Soilu-Hanninen et al, 2005 [67]	40 cases 40 controls		Lower levels in relapse than remission	Lower vitamin D levels in MS than controls during summer, but no differences in winter	Inverse relationship of vitamin D with MS activity; seasonal variation

MS: Multiple sclerosis; EDSS: Expanded disability status scale; RRMS: Relapsing-remitting MS; PPMS: Primary-progressive MS; URT: Upper respiratory tract.

concentrations of 25(OH)D, 1,25(OH)2D3 and parathyroid hormone (PTH) in 29 individuals with MS and 22 age- and sex-matched control volunteers demonstrated no significant differences in plasma PTH, 25 (OH)D and 1,25(OH)2D3 concentrations; however, women with MS had significantly higher 25(OH)D and 1,25(OH)2D3 concentrations than men with MS, suggesting that vitamin D requirements may differ between the sexes [64].

A study in 132 patients with MS (58 with relapsing remitting MS during remission, 34 during relapse and 40 primary progressive MS cases), and 60 healthy matched individuals showed significantly lower levels of 25(OH)D(3) and 1,25(OH)(2)D(3), in relapsing-remitting patients than in controls, especially during relapse [65]. Similarly, a study in 199 patients with MS, clinically isolated syndrome or tranverse myelitis showed that a large number of patients were deficient in vitamin D [66]. The lower vitamin D levels during MS relapses than in remission suggested that vitamin D could be involved in the regulation of the clinical disease activity of MS [67].

The average vitamin D level seems to be lower in winter compared to summer [68]. In a population-based cohort of 142 relapsing-remitting (RR) MS patients in Tasmania, Australia, it was found that relapse rates were inversely associated with prior erythemal ultraviolet radiation (EUV) and serum 25(OH)D levels [69]. Another study from the same area on 136 prevalent cases with MS and 272 age and sex matched controls found high prevalence of vitamin D insufficiency in MS cases and controls. Among MS cases, increasing disability was strongly associated with lower levels of 25(OH)D and with reduced sun exposure. Cases with higher disability (EDSS > 3) were more likely to have vitamin D deficiency than controls [70]. A longitudinal study in 23 patients with MS and in 23 healthy controls found that vitamin D deficiency (serum level of 25(OH)D < or = 37 nmol/l) was common, affecting half of the patients and controls at some time during the one year of observation, and although seasonal variation of 25(OH)D was similar in patients and controls, 25(OH)D serum levels were lower and intact PTH serum levels were higher during MS relapses than in remission [71].

In patients with MS associated with vitamin D deficiency, vitamin D intake should be sufficient to maintain year-round 25(OH)D levels between 55 -70 ng per mL [72]. Some investigators have recommended that prophylactic use of vitamin D is a viable option as an adjunct to conventional medicine for MS [73]. Although high doses of vitamin D(3) may be required for therapeutic efficacy, the serum concentration of 25-hydroxyvitamin D [25(OH)D] that does not cause hypercalcemia is not well defined. One mcg per day of vitamin D(3) (cholecalciferol) increases circulating 25(OH)D by about 1 nmol/L (0.4 ng/mL). A recommended dietary allowance (RDA) is the long-term daily intake level that meets the total requirements for the nutrient by nearly all healthy individuals (it would presume no sunshine). If 70 nmol/L is regarded as a minimum desirable target 25 (OH)D concentration, then current recommendations of 15 mcg per day do not meet the criterion of an RDA [74]. Thus, the oral dose necessary to achieve adequate serum 25(OH)D levels is probably much higher than the current recommendations of 5-15 mcg/d [75].

However, because vitamin D is potentially toxic, intake of > 25 mcg (1000 IU)/d has been avoided even though clinical evidence showed that the currently highest safe dose limit of 50 mcg (2000 IU)/d is too low to obtain the desired serum levels [76]. In a pilot study in 15 patients with relapsing-remitting MS with 1 relapse during the last 12 months, oral calcitriol (1,25-dihydroxyvitamin D3) was administered for 48 weeks with a target dose of 2.5 mcg/d. Hypercalcemia was developed in 4 patients (2 symptomatic) [77]. In another small study in 12 patients with MS 1200 mg elemental Ca/d in combination with progressively increasing doses of vitamin D3 were given (700 to 7000 mcg/wk) for 28 weeks. Patients' mean serum 25(OH)D concentrations reached twice the physiologic range without eliciting hypercalcemia or hypercalciuria, supporting that intake of pharmacologic doses of vitamin D3 beyond the current upper limit is safe [78]. A large retrospective study in a total of 199 patients included 40 MS patients that received either cholecalciferol (</=800 IU/day) or high dose ergocalciferol (50,000 IU/day for 7-10 days, followed by 50,000 IU weekly or biweekly). Optimal levels (>/=100 nmol/L) of 25(OH)D

was achieved in less than 40% of patients and high dose ergocalciferol was much more effective than cholecalciferol. The authors concluded that prospective studies are required to determine appropriate regimen, safety, and clinical efficacy of vitamin D replacement therapy [66].

8. Conclusions

Multiple sclerosis is associated with reduced bone mass and vitamin D deficiency. Low circulating levels of vitamin D are at least partially responsible for osteoporosis of MS patients and may be involved in the regulation of the clinical disease activity of MS. Polymorphisms of the vitamin D receptor have been linked to osteoporosis and MS. Because vitamin D is potentially toxic, intake of enough vitamin D to increase the serum level to a desired target has been avoided. Future large clinical trials should determine the true safe upper limit of vitamin D intake in order to obtain a therapeutic effect in MS patients. It is likely that future therapeutic intervention in MS will include administration of vitamin D in addition to other treatment modalities.

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