

Drug Information Rounds

The Role of Vitamin D in Multiple Sclerosis

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OBJECTIVE: To evaluate the literature about the role of vitamin D in the prevention and treatment of multiple sclerosis (MS).

DATA SOURCES: MEDLINE (1966–April 2006) and *International Pharmaceutical Abstracts* (1970–April 2006) searches were performed. In addition, pertinent references from identified articles were obtained. Key search terms included vitamin D, 25-hydroxyvitamin D, vitamin D deficiency, and multiple sclerosis.

DATA SYNTHESIS: Vitamin D supplementation prevented the development and progression of experimental autoimmune encephalitis, an animal model of MS, in mice. A large, prospective, cohort study found that vitamin D supplementation was associated with a 40% reduction in the risk of developing MS. Four small, noncontrolled studies suggested that vitamin D supplementation may decrease exacerbation of MS symptoms.

CONCLUSIONS: Vitamin D supplementation may help prevent the development of MS and may be a useful addition to therapy. However, current studies are in small populations and are confounded by other variables, such as additional vitamin and mineral supplementation.

KEY WORDS: multiple sclerosis, vitamin D.

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REQUEST

What is the role of vitamin D in the prevention and treatment of multiple sclerosis (MS)?

RESPONSE

BACKGROUND

MS is a chronic, progressive, autoimmune disease of the central nervous system (CNS) affecting approximately 400 000 Americans.¹ Symptoms of MS are dependent on the location of the CNS lesions and range from numbness and fatigue to muscle weakness and paralysis. The disease has 4 forms: primary progressive, with worsening of symptoms over time without acute exacerbations; relapsing–remitting, characterized by alternating periods of exacerbation and remission of symptoms; secondary progressive, starting as relapsing–remitting MS, then leading to a steady decline in function; and progressive–relapsing, which is similar to primary progressive MS, but with occasional exacerbations.²

Immunomodulators (interferon beta and glatiramer acetate) are recommended as first-line therapies in patients with MS. The immunosuppressant mitoxantrone also reduces the incidence of exacerbations but is considered a second-line therapy due to its adverse effect profile. Glucocorticoids are beneficial in shortening the duration of acute exacerbations but are not recommended for long-term use.² While the etiology of MS is unknown, it appears to be multifactorial and possibly related to genetics, viral infections, or environmental toxins. Issues relevant to this discussion on vitamin D include geographic factors, diet, and exposure to sunlight.³

Vitamin D (cholecalciferol) is a lipid-soluble vitamin synthesized by the conversion of 7-dehydrocholesterol to vitamin D in the skin. Exposure to ultraviolet (UV) B radiation is required for this reaction. A large US cohort study found that 3.5 times more women residing in northern states were diagnosed with MS, compared with women in southern states.⁴ MS is also more prevalent in areas reporting fewer than 2000 hours of sunshine annually.⁵ These findings are thought to be due to decreased exposure to UV radiation. MS displays seasonal variability, with highest disease activity in the spring and lowest in the fall.⁶ Because serum levels of 25-hydroxyvitamin D reflect the UV

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radiation exposure of the previous season, the increase in disease activity during the spring corresponds to the decrease in winter sunlight exposure.⁷ A Finnish study found that, compared with patients without MS, patients with MS had lower serum vitamin D levels during the summer.⁸ Therefore, it is possible that an association between MS and decreased vitamin D synthesis exists.

A link between dietary intake of vitamin D and the incidence of MS has also been suggested. Vitamin D can be obtained from diet sources such as fatty fish and fortified dairy products and cereal. The Atlantic coastal areas of Norway have a lower incidence of MS than the rest of Scandinavia, which is thought to be due to the high amount of vitamin D from fish in the local diet.⁹

Vitamin D, whether from diet or UV exposure, is inactive and may be stored in fat or converted by the liver to 25-hydroxyvitamin D. Serum levels of 25-hydroxyvitamin D are used to monitor vitamin D status. 25-Hydroxyvitamin D may be stored in the liver or further converted to the metabolically active form, 1,25-dihydroxyvitamin D₃ (calcitriol), by the kidneys.¹⁰ Mice treated with dietary 1,25-dihydroxyvitamin D₃ prior to induction of experimental autoimmune encephalomyelitis (EAE), an animal model for MS, did not develop symptoms of EAE, compared with 100% incidence in the control group.¹¹ In mice with EAE, 1,25-dihydroxyvitamin D₃ injections followed by dietary supplementation halted disease progression. The effects of vitamin D were reversible, as evidenced by EAE progression after discontinuation of the supplement. These findings suggest that the active form of vitamin D may be effective in treating patients with MS.

Vitamin D receptors are found in most body cells including neurons, oligodendrocytes, and astrocytes in the CNS. Vitamin D has many functions including influencing the immune response through the production of cytokines.¹⁰ Activation of vitamin D receptors decreases production of proinflammatory cytokines such as interleukin-2, interferon-gamma (INF- γ), and tumor necrosis factor- α . Production of antiinflammatory cytokines, such as interleukin-4 and transforming growth factor- β (TGF- β), is increased by vitamin D.¹⁰ TGF- β 1 was associated with symptom improvement in mice with EAE.^{10,12} Vitamin D may be beneficial in patients with MS due to its suppressive effects on the immune system.

VITAMIN D AND PREVENTION OF MULTIPLE SCLEROSIS

As of April 2006, there have been no studies evaluating vitamin D for the prevention of MS; however, data from 2 large, prospective cohort studies suggest that vitamin D may be beneficial as a prophylactic treatment. Dietary information obtained from the Nurses Health Study (NHS) and Nurses Health Study II (NHS II) was used to evaluate the effect of vitamin D supplementation on the risk of developing MS.¹³ Nurses aged 25–55 years living in the US

supplied data biennially on demographics, lifestyle habits including diet, and health including diagnosis of new diseases.¹⁴ The initial dietary questionnaires were conducted in 1980 for the NHS and in 1991 for the NHS II. Follow-up continued until the onset of MS symptoms, death, or completion of the study. The NHS ended in 1998, and the NHS II ended in 1999.¹³

Participants were questioned about use of vitamin D supplements, but not about the dose, which was assumed to be 400 IU (10 μ g). Information was also collected on dietary sources of vitamin D, such as skim/low-fat milk and fish, and the use of multivitamins. Participants were grouped into 5 quintiles based on intake of vitamin D from diet and supplements at baseline. Only the 187 563 women with complete baseline food frequency questionnaires were included in the analysis. Of these women, 173 were diagnosed with MS after baseline.¹³

Women with the highest vitamin D intake were more likely to be using a multivitamin; therefore, vitamin D intake was associated with the intake of other vitamins. Subjects with the highest vitamin D intake were less likely to develop MS (RR 0.67; 95% CI 0.4 to 1.12; *p* value for trend = 0.03). No association was found between dietary intake alone and the development of MS. Long-term use of a multivitamin (≥ 10 y) resulted in a 41% risk reduction compared with participants who had never used a multivitamin (95% CI 0.18 to 0.93). Controlling for age, smoking, and geographic latitude at birth did not affect these results. The authors concluded that women taking supplemental vitamin D had a 40% lower risk of developing MS than women not taking vitamin D.¹³

VITAMIN D AND TREATMENT OF MULTIPLE SCLEROSIS

The efficacy of vitamin D for treatment of MS has been examined in noncontrolled trials. The effect of calcium, magnesium, and vitamin D supplementation on relapse rate was evaluated in 16 patients with MS.¹⁵ The patients were 22–37 years old and had experienced an exacerbation of MS symptoms within 24 months prior to the study. Participants received magnesium 10 mg/kg, calcium 16 mg/kg, and cod liver oil 20 g supplying 5000 IU of vitamin D per day. The primary endpoint of the trial was the actual number of exacerbations compared with the expected number.

Exacerbations were defined as a period of at least 24 hours in which the patient experienced a worsening of symptoms when he or she had been stable or improving during the previous month. Based on patient histories, the expected number of exacerbations was 25. When the spontaneous decline in exacerbations usually seen with MS was considered, the expected number was 22. Six patients did not complete the study, and 10 participated for 11–24 months. There was a significant reduction in the actual number of exacerbations compared with the expected number (9 vs 25; *p* < 0.005 and 9 vs 22; *p* < 0.01). When

data from the 6 subjects who discontinued the study were included, the actual number of exacerbations was 14 and the expected number was 32 ($p < 0.005$). The authors concluded that calcium, magnesium, and vitamin D supplementation reduced the number of exacerbations experienced by patients with MS.¹⁵

An open-label study evaluated 1,25-hydroxyvitamin D₃ (calcitriol) treatment in 15 patients with relapsing–remitting MS.¹⁶ The patients were 22–44 years old, had experienced at least one exacerbation during the year prior to beginning the study, and were not being treated for MS. Patients who were predisposed to hypercalcemia, had renal insufficiency, or used digitalis were excluded from the study. Oral calcitriol was started at 0.5 µg daily and increased by 0.5 µg/day every 2 weeks until the target dosage of 2.5 µg/day was reached. Dietary and supplemental calcium intake was restricted to 800 mg daily. Steroid treatment of exacerbations was allowed during the study. Two participants withdrew due to development of hypercalcemia. Five exacerbations were reported in 4 (27%) patients completing the 48 week study. Fourteen patients were followed after discontinuation of calcitriol for a mean of 10 months; 7 experienced 9 exacerbations during that period. The authors suggested that calcitriol therapy was unlikely to aggravate symptoms of MS.

An open-label trial of alfacalcidol (activated vitamin D) was conducted in 5 patients with MS.¹⁷ The patients had relapsing–remitting MS, with a relatively low exacerbation rate, and received alfacalcidol 1.5 µg/day for 6 months. Three patients remained stable, 1 had improvement in neurologic status, and 1 developed an acute relapse. No adverse effects were reported with use of alfacalcidol.

A pilot study enrolled 11 patients with relapsing–remitting MS to determine the safety and efficacy of 19-nor-1,25-dihydroxyvitamin D₂, a vitamin D analog.¹⁸ Patients received 6 monthly magnetic resonance imaging (MRI) scans prior to starting treatment. After 19-nor-1,25-dihydroxyvitamin D₂ was titrated to the maximally tolerated dose (average 4 µg), participants received an additional 6 monthly MRI scans. While no adverse effects were reported, no significant changes were seen in clinical symptoms or MRI lesions.

DISCUSSION

The etiology of MS is complex, but vitamin D appears to play a role. Studies on EAE in mice suggest that vitamin D may be useful in the prevention and treatment of MS. Data from the NHS and NHS II support the theory that vitamin D may prevent MS; however, most of the participants received vitamin D from a multivitamin supplement, and the other vitamins and minerals may provide additional benefit. In addition, some of the participants reported using calcium supplements that may have included vitamin D, leading to an underestimation of their vitamin D intake.

However, the study results were not altered by exclusion of these participants from statistical analysis.¹³

There is little evidence to support the effectiveness of vitamin D in the treatment of MS. The results of 2 noncontrolled studies suggest that vitamin D may be helpful, but the small patient populations and confounding variables limit the usefulness of the data. Vitamin D was coadministered with calcium and magnesium in one trial, preventing determination of its actual effectiveness.¹⁵ In addition, the source of vitamin D used in that study, cod liver oil, also contains fatty acids, which may have contributed to the positive results. The second study used the activated form 1,25-hydroxyvitamin D₃ but was too small to make a definitive conclusion about the vitamin's efficacy.

19-Nor-1,25-dihydroxyvitamin D₂ was not effective in reducing relapse rates. Alfacalcidol shows potential for treatment of MS, but it is not available in the US. Larger studies conducted for a longer duration of time are needed to determine whether the drug is truly efficacious.

SUMMARY

Based on the geographic pattern and seasonal variation seen with MS, vitamin D supplementation and adequate exposure to sunlight should be recommended for healthy patients. Before vitamin D supplementation can be routinely recommended for either prevention or treatment of MS, the specific product, its effectiveness, and the optimal dose need to be determined in randomized, controlled studies with large sample sizes.

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REFERENCES

1. National Multiple Sclerosis Society. Just the facts: 2005–2006. www.nationalmssociety.org/Brochures-Just%20the.asp (accessed 2005 Jul 26).
2. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002; 58:169–78.
3. Kidd PM. Multiple sclerosis, an autoimmune inflammatory disease: prospects for its integrative management. *Altern Med Rev* 2001;6:540–66.
4. Hernán MA, Olek MJ, Ascherio A. Geographic variation of MS incidence in two prospective studies of US women. *Neurology* 1999;53:1711–8.
5. Leibowitz U, Sharon D, Alter M. Geographical considerations in multiple sclerosis. *Brain* 1967;90:871–86.
6. Auer DP, Schumann EM, Kümpfel T, Gössl C, Trenkwalder C. Seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis (letter). *Ann Neurol* 2000;47:276–7.
7. Saraiva GL, Cendoroglo MS, Ramos LR, et al. Influence of ultraviolet radiation on the production of 25 hydroxyvitamin D in the elderly population in the city of São Paulo (23° 34'S), Brazil. *Osteoporos Int* 2005;16: 1649–54. Epub 10 June 2005. DOI 10.1007/s00198-005-1895-3
8. Soilu-Hänninen M, Airas L, Mononen I, Heikkilä A, Viljanen M, Hänninen A. 25-Hydroxyvitamin D levels in serum at the onset of multiple sclerosis. *Multiple Sclerosis* 2005;11:266–71. DOI 10.1191/1352458505ms11570a

9. Hayes CE, Cantorna MT, DeLuca HF. Vitamin D and multiple sclerosis. *Proc Soc Exp Biol Med* 1997;216:21-7.
10. VanAmerongen BM, Dijkstra CD, Lips P, Polman CH. Multiple sclerosis and vitamin D: an update. *Eur J Clin Nutr* 2004;58:1095-109. Epub 31 Mar 2004. DOI 10.1038/sj.ejcn.1601952
11. Cantorna MT, Hayes CE, DeLuca HF. 1,25-Dihydroxyvitamin D₃ reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. *Proc Natl Acad Sci U S A* 1996;93:7861-4.
12. Mahon BD, Gordon SA, Cruz J, Cosman F, Cantorna MT. Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. *J Neuroimmunol* 2003;134:128-32.
13. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004;62:60-5.
14. Michels KB, Solomon CG, Hu FB, et al. Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study. *Diabetes Care* 2003;26:1752-8.
15. Goldberg P, Fleming MC, Picard EH. Multiple sclerosis: decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D. *Med Hypotheses* 1986;21:193-200.
16. Wingerchuk DM, Lesaux J, Rice GPA, Kremenchutzky M, Ebers GC. A pilot study of oral calcitriol (1,25-dihydroxyvitamin D₃) for relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2005;76:1294-6. DOI 10.1136/jnnp.2004.056499
17. Achiron A, Barak Y, Miron S, Izhak Y, Faibel M, Edelstein S. Alfacalcidol treatment in multiple sclerosis (letter). *Clin Neuropharmacol* 2003;26:53.
18. Fleming JO, Hummel AL, Beinlich BR, et al. Vitamin D treatment of relapsing-remitting multiple sclerosis (RRMS): a MRI-based pilot study (abstract). *Neurology* 2000;54(suppl 3):A338.

EXTRACTO

OBJETIVO: Evaluar la literatura sobre el rol de la vitamina D en la prevención y tratamiento de esclerosis múltiple, por sus siglas en inglés, MS (multiple sclerosis).

FUENTES DE INFORMACIÓN: Se hicieron búsquedas de la literatura biomédica a través del motor de búsqueda de información médica por Internet Medline para las fechas de 1966-abril 2006 y en los *Extractos Farmacéuticos Internacionales*, conocido por sus siglas en inglés como IPA (*International Pharmaceutical Abstracts*) de 1970-abril 2006. Además, se utilizaron las referencias los artículos identificados. Los términos de búsqueda utilizados incluyeron vitamina D, 25-hidroxivitamina D, deficiencia de vitamina D, y esclerosis múltiple.

SÍNTESIS: La suplementación con vitamina D previene el desarrollo y progreso de encefalitis autoinmune experimental, un modelo animal de MS, en ratón. Un estudio grande prospectivo de cohorte encontró que la suplementación con vitamina D se asociaba con una disminución en la probabilidad de desarrollar MS. Cuatro pequeños estudios no controlados, sugieren que la suplementación con vitamina D puede disminuir la exacerbación de los síntomas de MS.

CONCLUSIONES: La suplementación con vitamina D puede ayudar a prevenir el desarrollo de MS y puede ser útil añadirlo en su tratamiento. Sin embargo, la mayor parte de los estudios actuales se han llevado a cabo en poblaciones pequeñas y sus resultados pueden ser influenciados por otras variables tales como el uso de suplementación adicional con vitaminas y minerales.

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RÉSUMÉ

OBJECTIF: Evaluer la littérature relative au rôle de la vitamine D dans la prévention et dans le traitement de la sclérose en plaques (SEP).

SOURCES DES DONNÉES: Il a été conduit une revue de la littérature à partir de MEDLINE (1966 à avril 2006) et d'International Pharmaceutical Abstracts (IPA) (1970 à avril 2006). Les références pertinentes des articles repérés ont aussi été utilisées. Mots-clés employés: vitamin D, 25-hydroxyvitamin D, vitamin D deficiency, et multiple sclerosis.

SYNTHESE DES DONNÉES: La supplémentation en vitamine D a prévenu le développement et la progression de l'encéphalite auto-immune expérimentale de la souris, un modèle animal de SEP. Une cohorte prospective de grand effectif a montré que la supplémentation en vitamine D chez la femme était associée à une probabilité réduite de développer une SEP. Quatre études non contrôlées et de très faibles effectifs suggèrent que la supplémentation en vitamine D est susceptible de diminuer le nombre de poussées de SEP.

CONCLUSIONS: La vitamine D est susceptible de prévenir le développement de la SEP et serait un complément utile au traitement de cette maladie. Cependant, les études disponibles se réfèrent à des populations réduites et présentent des facteurs de confusion par d'autres variables, comme la supplémentation par d'autres vitamines ou des minéraux.

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