

Mellen Center Approaches: Multiple Sclerosis and Vitamin D

What is Vitamin D?

Vitamin D is fat soluble vitamin. It helps regulate calcium metabolism. It is important in promoting absorption of calcium/phosphorus in the gut to support bone integrity. Vitamin D is synthesized by the skin from sunlight. Vitamin D needs to undergo conversion from its inert state by process of hydroxylation initially in the liver

converting to 25-hydroxyvitamin D(25 OH D) and then in the kidney which produces the active form 1,25 dihydroxy vitamin D (calcitriol). Vitamin D is also found in certain foods and pill supplements. A wide array of clinical and basic science literature has established the importance of adequate levels of vitamin D in the prevention of rickets in children, and osteoporosis, osteopenia, hip fracture and osteomalacia in older adults

In addition to this well-established connection between vitamin D and calcium metabolism, Vitamin D deficiency has been linked to Type-I diabetes, Alzheimer's disease and other dementias, depression, schizophrenia, and some infectious diseases as commonplace as bacterial vaginosis. In many instances, the link has been established by association, however there is an active body of research conducting randomized clinical trials and establishing causative links.

What are the implications for monitoring Vitamin D?

In the United States there is an increased incidence of bone fractures especially in the elderly populations. Hip fracture is second to stroke as a major cause of disability and nursing home placements. MS patients are at higher risk for osteopenia/osteoporosis especially if they have gait dysfunction, are wheelchair or bed bound, have had courses of IV steroids or if they are on low dose oral steroids. MS patients tend

to stay out of the sunlight because of heat sensitivity further increasing the risk for Vitamin D deficiency. There have been studies that suggest Vitamin D deficiency may play a role in immune system function and the development of auto immune disorders such as Multiple Sclerosis. There has also been increasing evidence that deficiency may also increase risk for developing cardiovascular disease and certain types of cancers- such as uterine, breast, prostate, colon.

What research has been done to investigate Multiple Sclerosis and Vitamin D deficiency?

Animal studies have been able to demonstrate that EAE (experimental autoimmune encephalomyelitis) could not be elicited in mice that had sufficient Vitamin D levels. It is theorized that the amount of sunlight exposure affects the production of Vitamin D and the hormonal form of Vitamin D may be a selective immune regulator and potentially could inhibit the development of the disease. Some studies indicate that relapse rates were decreased in MS patients taking higher oral supplements of Vitamin D but the data is limited. There have been retrospective studies that suggest that EDSS (Expanded Disability Status Scale) scores increased in patients that had Vitamin D deficiency. A recent study done in Australia indicates that sunlight exposure and Vitamin D intake may be independent factors affecting risk for CNS demyelination. There is currently a significant interest in Vitamin D and researchers are continuing to study what role Vitamin D may play in diseases including Multiple Sclerosis. For example, evidence points to the direct and indirect regulation of T cell development and function by vitamin D. In animal models, in the absence of vitamin D and signals delivered through the vitamin D receptor, auto reactive T cells develop and in the presence of active vitamin D (1,25(OH)₂D₃) and a functional vitamin D receptor the balance

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in the T cell response is restored and autoimmunity avoided.

Is Vitamin D deficiency the cause of Multiple Sclerosis?

There is currently no evidence that this vitamin deficiency is the cause of Multiple Sclerosis. There has been increased interest that Vitamin D deficiency is prevalent in areas where there is less sunlight exposure and being further away from the equator in both directions. We also know that Multiple Sclerosis is more often found in northern climates (above 40 degrees latitude). The highest incidence of Multiple Sclerosis is found in Scandinavian countries where there is lower sunlight exposure. The correlation of decreased sunlight and decreased Vitamin D synthesis in immune system function is not fully understood at this time.

How is Vitamin D deficiency detected?

There are 2 forms that can be detected in the blood:

- 1) The current recommendation is to order serum 25-OH D (Vit D 25 hydroxy). 25-Hydroxyvitamin D is the major form found in the blood. It has a longer half life and concentration than 1,25 OH-D. It is commonly tested to assess Vitamin D status. It is not affected by PTH (parathyroid hormone) levels.
- 2) 1,25 OH-D 1,25 dihydroxyvitamin D 1,25(OH)₂D is a less accurate representation of Vit D status.

Vit D (25-OH D) results

Deficiency	<20 ng/ml
Insufficient	20-29 ng/ml
Sufficient	30 ng/ml
Toxic	>150 ng/ml

Many labs do not report Vit D2 or Vit D 3 levels separately. Some labs do report them separately and then give a total Vit 25 hydroxy level by combining both Vit D2 and D3 scores.

The cost of Vit D 25 hydroxy level at CCF is approximately \$201 dollars.

More than 50% of women and 40% of men have Vit D deficiency (N Engl J. Med 2007,357(3):266-81.). This may be higher in Northeastern Ohio.

What are the sources of Vitamin D and current RDA?

Two sources of Vitamin D: exogenous (ingested Vit D from foods and supplements) and endogenous (from sunlight). Since Vitamin D is fat soluble, toxicity can occur at high levels of oral intake of supplements.

There are no strict guidelines on Vit D supplements, many are anecdotally based. Vitamin D supplements come in 2 forms: Vitamin D3 (cholecalciferol) and Vitamin D 2 (ergocalciferol)

Vitamin D can be obtained from sunlight exposure (10-15 min daily exposing both forearms)

Vitamin D 2 or Vitamin D 3 supplements:

Food sources: Fatty fish such as salmon, mackerel, tuna, sardines. Orange juice and milk supplemented/fortified with Vit D.

Who should be considered for Vitamin D deficiency?

Multiple Sclerosis patients should be considered and especially, marginally ambulatory or nonambulatory patients.

- Elderly patients
- Patients that have other co-morbidities like cancer, any additional auto immune disorder.
- Endocrine disorders like hyperparathyroidism
- Patients that have had fractures
- Any patient on long term steroid tx.
- African American ,Hispanic patients as darker skinned people have decreased absorption of Vitamin D from sunlight exposure.
- Gastric bypass patients

Who should not be considered for Vitamin D supplementation?

Patients with hypercalcemia, hypervitaminosis D, malabsorption syndrome, decreased renal function. Caution needs to be exercised with use of Vitamin D supplements in patients with heart disease, renal calculi, or arterosclerosis.

If patients may have hyperparathyroidism they should be evaluated before higher doses of vitamin D supplementation are implemented.

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How is Vitamin D deficiency supplementation dosed?

Dr R. Marrie Director of Multiple Sclerosis Clinic in Winnipeg Canada reports that because of the high cost of prescription strength (Vit D 50,000 IU) in Canada the preferred method at several Canadian Multiple Sclerosis ,Rheumatology and Inflammatory Bowel clinics is to place 100% of their patients on Vit D 2000 IU daily without checking a level first.

Patients stay on this supplement for 4 months and then Vit D hydroxyl level is checked. On this dose toxicity is generally avoided and reportedly 75% of their patients are adequately supplemented. If the level is nearly normal the dose is increased to 3000 IU daily and if quite low then dose is 4000 IU daily and make referral to dietician. Once the Vitamin D level is normal they do not re-check the levels annually. We are planning to use this method primarily at the Mellen Center due to it's practicality, lower cost, and efficiency.

Note that taking Vitamin D with food enhances absorption.

Note that the American Academy of Neurology multiple sclerosis subcommittee recently reviewed literature on Vitamin D deficiency and MS and recommended a wide range of doses from 300-4000 units per day of Vitamin D3.

The current Institute of Medicine recommendations are felt by many doctors to be insufficient to help maintain adequate Vitamin D levels.

An alternative approach:

Dr Chad Deal at Cleveland Clinic Metabolic Bone Clinic has developed guidelines based on his clinical expertise and recommends the following: (CCF Smartset-Spine Metabolic Bone)

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| If level < 10 ng | Vit D 2 - 50,000 IU - 1 tab qd x 14 days, then 2 tabs a week x 2 months, then 2 tabs per month on the 1st and 15th |
| If level 10-20ng | Vit D2 - 50,000 IU - 2 tabs a week x 2 months, then 2 tabs per month |
| If level 20-25ng | Vit D2 - 50,000 IU - 1 tab weekly x 2 months, then 2 tabs per month |
| If level 25-30 ng | Vit D3 - 2000 IU tab daily |
| If level 31-40 | Vit D3 - 1000 IU tab daily |

What effect can be expected from addressing deficiency of Vitamin D?

Supplementation will help prevent loss of bone integrity, decrease risks for fractures There have been patient reports of improvement with fatigue or a decreased perception of pain. Some patients do not have any visible effect but there may be a benefit to immune system function reducing auto immune disorders, cancer and cardiovascular risks .

What should be taken into consideration prior to starting Vit D supplementation?

- Pregnant patients, patients planning to become pregnant, nursing mothers - Vit D at 50,000 IU weekly is pregnancy risk category C (dose exceeds RDA).
- Pregnancy risk category A if dose is the recommended RDA and is not exceeded
- Supplements patients are taking in multivitamins, calcium and OTC Vitamin D
- Other medication interactions: Antacids may cause hypermagnesemia, Cardiac glycosides may increase risk for arrhythmias, verapamil increase risk for A fib – monitor calcium levels closely. Corticosteroids may antagonize effect of Vit D. Phenobarbital, Phenytoin(Dilantin) may increase Vitamin D metabolism, decrease effectiveness

What are the signs of Vitamin D Toxicity?

- weakness
- weight loss
- vertigo
- decreased appetite/anorexia
- nausea,vomiting
- diarrhea
- constipation
- abdominal cramping
- dry mouth
- excess thirst
- excess urine
- headache
- lethargy
- muscle or bone pain

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Should Multiple Sclerosis patients take Vitamin D supplements ?

At the Mellen Center we feel that the preponderance of accumulated data means that we should be focusing on vitamin D supplementation and recommend trying to get patients into the normal range of vitamin D levels unless there are countervailing contraindications.

More research is being done and prospective and longitudinal studies may help provide a more comprehensive understanding of any cause and effect relationship of Vitamin D deficiency and immune system functions.

REFERENCES:

- Ascherio A, Munger KL, Simon KC. Vitamin D and multiple sclerosis. *Lancet Neurology* 2010; 9 (6) 599-612.
- Banwell B, et al. Incidence of acquired demyelination of the CNS in Canadian children. *Neurology* 2009;72:232-239.
- Burton JM, Kimball S, Vieth R, et al. A phase I/II dose escalation trial of vitamin D3 and calcium in multiple sclerosis. *Neurology* 2010; 74(23) 1852-1859. [Pub Med]
- Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. *Prog Biophys Mol Biol.* 2006 Sep;92(1):60-4. Epub 2006 Feb 28.
- Correale J, Ysraelit MC, Gaitan MI. Immunomodulatory effects of vitamin D in multiple sclerosis. *Brain* 2009; 132: 1146-1160.
- Lucas RM, Ponsonby AL, Dean K, et al. Sun exposure and vitamin D are independent risk factors for CNS demyelination. *Neurology* 2011;76: 540-547.
- Pepper KJ, Judd SE, Nanes MS, Tangpricha V. Evaluation of vitamin D repletion regimens to correct vitamin D status in adults. *Endocrine Practice* 2009;15(2): 95-103.
- Pierrot-Deseilligny C. Clinical implications of a possible role of vitamin D in multiple sclerosis. *Journal of Neurology* 2009; 256: 1468-1479.
- Smolders J, Damoiseaux J, Menheere P, Hupperts R. Vitamin D as an immune modulator in multiple sclerosis, a review. *Journal of Neuroimmunology* 2008; 194(1-2): 7-17. [PubMed].
- Van Amerongen BM, Dijkstra CD, Lips P, Polman CH. Multiple Sclerosis and Vitamin D –a review. *European Journal of Clinical Nutrition* 2004; 58: 1095-1109.
- Vitamin D Consensus Statement (Clinical judgment supersedes this guideline) APPROVED: Medicine Institute Clinical Practice Committee, February 2010