Mellen Center Approaches: Multiple Sclerosis and Vitamin D

Q: What is vitamin D?

A**:** Vitamin D is fat soluble pro- hormone secosteroid (one carbon ring difference from a steroid) which controls over 200 genes. Vitamin D has effects on calcium metabolism, modulation of the immune system, pancreatic function, vascular/endothelial function, cardiac function, nervous system function, muscle function, intestinal function, among others. Vitamin D is necessary in all stages of life. Although considered a vitamin, vitamin D is mainly synthesized in our body with only a small contribution from exogenous intake. It was initially recognized for its role in promoting absorption of calcium/phosphorus in the gut to support bone integrity.

Q: How is vitamin D made and are there different types of vitamin D?

A: Vitamin D is synthesized by the skin through the effects of sunlight on a cholesterol derivative (7-dehydrocholesterol). Vitamin D_3 (cholecalciferol) is the natural form of vitamin D made by our skin. Vitamin D_2 (ergocalciferol) is a plant based form of vitamin D, which can be ingested. 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 (1,25 $(OH)_2$ D or calcitriol). Vitamin D_2 is found in certain foods and vegetarian pill supplements. Vitamin D_3 is also available as a supplement and is synthesized using animal 7-dehydrocholesterol.

Q: Why is vitamin D important?

A. Vitamin D acts through the vitamin D receptor (VDR) which is extensively expressed in several cell lines in most body systems. 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, autoimmune diseases, 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 investigating causative links.

Q: What is the evidence for the role of vitamin D in multiple sclerosis (MS)?

A significant amount of epidemiological data support the role of vitamin D in MS. The observed gradient in MS prevalence in northern latitudes has been hypothesized to occur as a result of lower sunlight exposure and lower vitamin D levels. It is theorized that the amount of sunlight exposure affects the production of vitamin D and may be a selective immune regulator and potentially could inhibit the development of the disease. A growing body of evidence indicates that low vitamin d levels may be a risk factor for MS. These include studies showing that MS patients have lower vitamin D levels compared to

controls; during relapses vitamin d levels are lower when compared to clinically stable state; and low vitamin D has been shown to be a predictor of greater clinical disability. There have been retrospective studies that suggest that the Expanded Disability Status Scale (EDSS) scores are partially predicted by vitamin D deficiency. In pediatric MS vitamin d has been associated with increased relapse rate and Vitamin D levels also seem to modulate effects of disease modifying agents most notably beta-interferon compounds.

Q: Is Vitamin D deficiency the cause of MS?

A: There is currently no direct evidence that vitamin D deficiency is the cause of MS. Several studies have demonstrated that low vitamin D levels in utero and during life may be a risk factor for MS There has been increased interest as 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 MS is more often found in northern climates (above 40 degrees latitude). Some of the highest incidence areas of MS are 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.

Q: What is the evidence for vitamin D supplementation in MS?

A: There is currently insufficient evidence regarding the efficacy of vitamin D in persons with MS. Several smaller sized studies have failed to show an effect of vitamin D on efficacy outcomes in MS. However these studies have been limited by small sample sizes, varying doses of vitamin D, and methodological issues. A large randomized study of 229 participants with relapsing remitting MS (SOLAR Trial) missed its primary endpoint (Smolders, ECTRIMS 2016). Although the primary outcome (disease activity free state) did not reach significance, several MRI measures including combined unique lesions did. A large multi-center study of vitamin D as an add-on to glatiramer acetate was funded by the National Multiple Sclerosis Society (NCT01490502).

The ability of vitamin D supplementation to prevent MS in healthy individuals is even more complex and may require very large observational studies. A recent study using Mendelian randomization found that genetically lowered 25 (OH) D levels increased susceptibility to MS.

Q: What are the mechanisms through which vitamin D might exert it effects in MS?

A: Basic science studies have been able to demonstrate that the animal model of MS, EAE (experimental autoimmune encephalomyelitis), could not be elicited in mice that had sufficient vitamin D levels. 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 the absence of signals delivered through the vitamin D receptor, auto reactive T cells develop. In the presence of active vitamin D ($1,25\ (OH)_2$ D) with a functional vitamin D receptor the balance in the T cell response is restored and autoimmunity

avoided. Vitamin D is also known to have neuroprotective effects in several cells types within the central nervous system, and is thought to act mainly through neurotrophic factors.

Q: Is it important to determine vitamin D status and how is testing conducted?

A: The purpose of testing vitamin D is to establish the level of sufficiency and also to monitor the effects of vitamin D supplementation. Testing is needed to help calculate the initial dose to be used and to follow levels after supplementation given significant variability in response to oral vitamin d supplementation. Although some groups have advocated treating without testing a level, we consider testing important to help guide rational selection of supplementation doses.

Vitamin D can be tested from serum (blood) samples. The most widely available test is that of the inactive form of vitamin D: 25 (OH) D. Although the active from (1, 25 $(OH)_2$ D) can be tested for also, its blood level is not reliable for determination of vitamin D deficiency. Although D_2 and D_3 levels may be measured separately total levels are most useful. The following guidelines have been used for interpretation of 25 (OH) D levels:

Vitamin D (25 (OH) D) results

Deficiency	<20 ng/ml
Insufficient	20-29 ng/ml
Sufficient	30 ng/ml
Toxic	>100 ng/ml

The levels of vitamin d considered for sufficiency are mainly based on bone effects of vitamin d and were established among indoor workers. The optimal level of vitamin D is probably significantly higher than the sufficiency level of 30 ng/ml, but an exact number is not known. At the Mellen Center most practitioners aim for levels between 40 and 70 ng/ml. The cost of a vitamin D 25 (OH) level at Cleveland Clinic is approximately $219 dollars. More than 50% of women and 40% of men have vitamin D deficiency. This may be higher in Northeastern Ohio.

Q: Should all MS patients have vitamin D levels monitored?

A. At the Mellen Center many patients are screened both initially and during periodic follow-up for vitamin D levels. The exact frequency of testing has not been formally evaluated in scientific studies. Yearly testing of vitamin D levels now forms part of the standard wellness approach developed at the Mellen Center. Vitamin D levels will vary seasonally in relation to sun exposure, and this should be considered when interpreting test results. The rationale for testing is based on possible protective effects related to the immune modulation properties of vitamin D, but also in relation to general health and bone health specifically. 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 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.

Q: Should vitamin D be supplemented?

A. Vitamin D supplementation can be conducted either empirically or based on serum levels tested in blood (see below). There are no specific data guiding either testing or dosage of supplementation. Given the relative high frequency of vitamin D deficient patients in the United States some group have advocated started vitamin D on all MS patients. Given the wide availability of 25 (OH) D testing, and the significant variability in serum levels, supplementation based on serum levels is most widely used at our center. The low cost and favorable safety profile of vitamin D are factors favoring supplementation.

Q: What type of supplement can be given?

Vitamin D can be replaced both using the plant form of vitamin D: D_2 (ergocalciferol) or the naturally occurring form: D_3 (cholecalciferol). Although D_2 and D_3 compounds have been considered therapeutically equivalent, multiple studies have shown D_3 produces a more robust increased in 25 (OH) D levels and is the preferred form used at the Mellen Center. Finally exposure to natural sunlight will also raise 25 (OH) D levels, but this is limited in winter months due to the zenith angle of the sun and also is limited in individuals with more skin pigmentation.

Q: What is the recommended dietary allowance (RDA) of vitamin D and how should deficiency be supplemented?

The current RDA recommended by the Institute of Medicine and the Food and Nutrition Board for vitamin D is of 600 international units (IU) daily. This dose was established for sufficiency to ensure bone and calcium homeostasis. Many MS experts consider this dose below what most patients need to ensure protective effects from the other mechanisms of vitamin D.

The approach for supplementation of vitamin D at the Mellen Center is based on the initial vitamin D level, and targets levels between 40 and 70 ng/ml, although the ideal vitamin D level remains unknown. Repeat testing and dosing adjustment is conducted annually or can be conducted after several months of supplementation to assure optimal levels have been reached.

30 ng/ml or below:

50,000 IU of vitamin D_2 or D_3 (large doses of vitamin D_2 are more easily found than D_3) weekly for 6 weeks by mouth followed by a daily dose between 3000 and 5000 IU of Vitamin D_3 by mouth.

Above 30 ng/ml
Between 2000 and 5000 IU of vitamin D_3 by mouth daily.

Q: Are there any contraindications to Vitamin D supplementation?

A: Patients with hypercalcemia, hypervitaminosis D, malabsorption syndrome (including gastric bypass surgery), decreased renal function. Caution needs to be exercised with use of vitamin D supplements in patients with heart disease, renal calculi, or arteriosclerosis.

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

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

A: 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.

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

A: The use of high doses of vitamin D in pregnancy and lactation remains an open question. The American College of Obstetrics and Gynecology considers doses of between 1000-2000 IU to be safe with most experts agreeing that despite lacking safety data in pregnancy doses of up to 4000 IU are also safe.
Cardiac glycosides-may increase risk for arrhythmias, verapamil increases the risk for atrial fibrillation, therefore monitoring calcium levels should be considered.
Corticosteroids may antagonize the effect of vitamin D.
Phenobarbital, phenytoin (Dilantin) may increase vitamin D metabolism and decrease effectiveness.

Q: What are the signs of vitamin D Toxicity?

A: Weakness, weight loss, vertigo, decreased appetite/anorexia, nausea, vomiting, diarrhea, constipation, abdominal cramping, dry mouth, excess thirst, excess urine, headache, lethargy, and muscle or bone pain.

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