A 35-year-old woman has relapsing remitting multiple sclerosis doing well on immunotherapy. Should she and other multiple sclerosis patients have their Vitamin D3 levels routinely checked? Would she and other MS patients benefit from Vitamin D3 supplementation? If so, how much? What might be the effect on the immune system? Should calcium be added and, if so, specifically what dose? Should Vitamin D3 level be measured on supplementation? What level is too high? What side effects might occur from D3 and calcium supplementation?

Discussion: Possible Influence of Vitamin D

Although the etiology of multiple sclerosis remains unknown, most cite a genetic susceptibility upon which an environmental trigger acts to initiate an autoimmune process of CNS damage. The role of vitamin D has become central to these discussions over the past few years. Evidence from epidemiologic studies of geographic distribution, sun exposure and vitamin D intake, as well as experimental animal models of MS, indicate a possible influence of vitamin D on disease susceptibility. There is also some evidence of possible disease modifying properties of vitamin D in MS.

Vitamin D (cholecalciferol) in humans is obtained from the diet and supplements or synthesis in the skin by ultraviolet B radiation (sunlight) conversion of 7-dehydrocholesterol (pre-vitamin D). The average vitamin D intake in the US is less than 400 IU/day, and most Americans have vitamin D levels in the deficient or insufficient range. One day of whole-body sun exposure is equivalent to a single dose of 10,000-25,000 IU vitamin D. Vitamin D is hydroxylated in the liver to 25-hydroxy vitamin D (25(OH)D), the major circulating form of vitamin D that reflects vitamin D status in the body. 25(OH)D is further converted to the hormonally active form 1,25-dihydroxy vitamin D (1,25(OH)2D) in the kidneys. Vitamin D and parathyroid hormone regulate calcium homeostasis by cellular uptake and renal retention. The optimal serum levels of 25(OH)D should be at least 75nmol/L, but preferably 90-100nmol/L. A daily dose of 1,000 IU vitamin D is needed to bring concentrations up to 75nmol/L 25(OH)D in 50 percent of the population, but as much as 4,000 IU/day to bring about 90 percent of healthy young adults to a level of more than 75nmol/L. Daily intake of 4,000-10,000 IU/day seems to be safe in young adults.

Sunlight exposure and dietary intake thus play an important role in vitamin D status. Skin color, gender, age and body fat also play a role. Elderly and dark skinned people produce less sunlight-induced vitamin D. Body fat absorbs vitamin D and influences serum 25(OH)D. Men tend to have higher levels than women. These facts may play a role in recommendations regarding supplementation.

There are several lines of evidence supporting the importance of vitamin D in MS. Inverse correlation between MS prevalence and sunlight has been reported. This may in part explain the much discussed North/South gradient in MS. A study of American military personnel showed that low 25(OH)D levels in adolescence may be associated with an increased risk of developing MS later in life. A 41 percent decrease

Vitamin D and MS: Implications for Patient Care

There are clear non-neurologic medical reasons to avoid hypovitaminosis D and some evidence that vitamin D supplementation can influence the course of MS in deficient patients.

By George J. Hutton, MD
of incidence of MS for every 50nmol/L increase in 25(OH)D was estimated for the white population. Low serum 25(OH)D levels have been reported in 50-70 percent of different MS populations.

Lower vitamin D levels have been reported during relapses in relapsing-remitting MS patients, and high vitamin D levels have been associated to low relapse activity. A recent report showed that children developing MS after presenting with a clinically isolated syndrome (CIS) had significantly lower serum levels of 25(OH)D compared to those that did not develop MS.

Most of the biologic effects of 1,25(OH)2D are mediated by the vitamin D receptor. This induces receptor mediated anti-inflammatory processes by reducing expression of MHC class II, surface co-stimulatory molecules and pro-inflammatory cytokines in monocytes/antigen presenting cells. It also inhibits T- and B-lymphocyte proliferation, reduces expression of pro-inflammatory cytokines, and induces apoptosis of activated T lymphocytes.

Evidence is beginning to accumulate of a complex interaction between genetic susceptibility to MS and the role of vitamin D. Expression of the MS associated HLA class II allele is influenced by vitamin D. Certain vitamin D receptor (VDR) gene polymorphisms have been shown to have an influence on disease susceptibility. Other VDR gene polymorphisms have been shown to influence disability progression in MS patients independent of sunlight exposure.

The serum component of vitamin D that is best to measure is 25(OH)D, with a half-life of several weeks. This measurement is representative of an individual’s overall vitamin D status. The internationally accepted norms fall between 75 and 200nmol/L with insufficiency existing below 75nmol/L and deficiency below 25nmol/L. The 75nmol/L level corresponds to the serum level below which the parathyroid hormone is stimulated by lack of vitamin D and below which osteoporosis becomes frequent. Although 1,25(OH)2D serum levels can be obtained, these are not as useful as the half-life is only four to six hours.

Much of the recent excitement regarding the role of vitamin D in MS can be traced to a Canadian study that was recently reported at several meetings. This story was picked up by medical and lay press and widely discussed. In this study, 50 MS patients were randomized into one of two groups: the treatment group took vitamin D in an escalating dose up to 40,000 IU/day while the control group were allowed to take their usual regimen (up to 4,000 IU/day). Based on the dose escalation, the treatment group took a mean of 14,000 IU/day over the course of the one-year study. All subjects also took calcium phosphate at 1,200mg per day. This was primarily a safety study, with some clinical endpoints as secondary outcomes.

The main outcome was that the subjects had no hypercalcemia, hypercalciuria or parathyroid dysfunction, despite having mean serum 25(OH)D values peaking at over 400 nmol/L. A widely published secondary outcome was that the treatment group had fewer relapses with a 41 percent reduction in annualized relapse rate, compared with a reduction of 17 percent in the control group. However, the study was not powered to assess clinical outcomes.

**Clinical Options**

So where does this leave us with respect to the use of vitamin D supplementation in our MS patients? Whether one fully accepts the above data as supporting the role of vitamin D supplementation in MS or

### Addressing Vitamin D Sufficiency

- The best indicator of vitamin D status is serum 25(OH)D.
- Internationally accepted norms fall between 75 and 200nmol/L:
  - Insufficiency exists below 75nmol/L. Deficiency exists below 25nmol/L.
  - 75nmol/L is the serum level below which the parathyroid hormone is stimulated by lack of vitamin D and below which osteoporosis becomes frequent.
- Supplementation options include OTC vitamin D₃ (available in doses up to 2,000 IU) or prescription vitamin D₂ (ergocalciferol, available as 50,000 IU).
- Most patients can be sufficiently supplemented with oral OTC vitamin D₃ 4,000 IU daily.
not, there are clear non-neurologic medical reasons to avoid hypovitaminosis D. Therefore, there is good rationale to check vitamin D serum status in MS patients, which is best accomplished by checking serum 25(OH)D. When insufficient or deficient levels are found, supplementation options include OTC vitamin D₃, commonly available in doses up to 2,000 IU or prescription vitamin D₂ (ergocalciferol), available as 50,000 IU orally. A useful guideline is that most patients can be sufficiently supplemented with oral OTC vitamin D₃ 4,000 IU daily.

It is important before starting this treatment to check that there is no hypercalcemia and to monitor vitamin D and calcium levels after several months of supplementation. One need not fear hypercalcemia or “vitamin D intoxication” if the patient has normal or low calcium before supplementation, and if one uses doses less than 10,000 IU/day. If hypercalcemia were to develop, one might expect signs to include neurologic ones, such as muscle twitching, weakness and depression, among others, but this is not expected with these moderate levels of supplementation. Some advocate adding calcium supplement of 1,200 mg daily as there is evidence that vitamin D and calcium work synergistically. Even those with 25(OH)D levels above 80nmol/L should be maintained on supplementation, and if one uses doses less than 10,000 IU/orally. A useful guideline is that most patients can be sufficiently supplemented with oral OTC vitamin D₃ 4,000 IU daily.

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