



**National  
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# *Clinical Bulletin*

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## **Vitamin D and MS: Implications for Clinical Practice**

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### **INTRODUCTION**

Recent studies have significantly changed our understanding of the effects of vitamin D on the body and on human health. In the past, it was assumed that most people have adequate vitamin D levels and that the effects of vitamin D are restricted to regulating calcium absorption and maintaining bone health. However, studies over the past decade have proven that these views are incorrect.

It is now recognized that there is an epidemic of vitamin D deficiency in many countries, including the United States. Furthermore, it is now known that, in addition to its effects on bones and calcium, vitamin D exerts important “non-skeletal” effects on many other body systems. There is growing concern that the widespread deficiency of this important vitamin may be contributing to significant public health problems by increasing the risk and the severity of many diseases, including multiple sclerosis (MS).

Since vitamin D has multiple actions on the body, clinicians who want to be well informed in this area must become knowledgeable about the neurological as well as non-neurological aspects of vitamin D and vitamin D deficiency. This information is essential for properly addressing vitamin D issues in the day-to-day clinical care of people with MS.

### **THE BASICS OF VITAMIN D**

Vitamin D is a hormone as well as a vitamin. It is often referred to as the “sunshine vitamin” because sun exposure is crucial for the body to synthesize the active form of vitamin D. In addition to its formation in the body, vitamin D may also be consumed orally through foods and dietary supplements. Very few foods, most notably oily fish (such as salmon), naturally contain significant amounts of vitamin D. In the United States, a limited number of other foods, including dairy products, cereals, and orange juice, are fortified with vitamin D (Holick, 2007, 2008; Moyad, 2008).

## **Determining Vitamin D Levels**

Levels of various forms of vitamin D may be determined with blood tests. The form of vitamin D that is most indicative of vitamin D status, and thus most reliable for diagnosing vitamin D deficiency, is “25-hydroxyvitamin D.” There are three general categories of 25-hydroxyvitamin D levels. “Sufficient levels” are those that are in the normal range, which is generally 30–100 ng/mL (75–250 nmol/L). Some have argued that the lower end of the normal range should be 35–40 ng/mL (Moyad, 2008). Levels that are mildly decreased, in the 20–30 ng/mL range, are referred to as “insufficient,” while those that are severely reduced, below 20 ng/mL are “deficient” (Holick, 2007, 2008).

## **Vitamin D and Calcium**

Vitamin D and calcium work together in many biological processes. Vitamin D is essential for the efficient intestinal absorption of calcium. Low blood levels of calcium lead to increased vitamin D levels, which then increase intestinal absorption as well as renal resorption of calcium. When taken with calcium, vitamin D appears to minimize loss of bone mineral density (Fragakis, 2003; Jellin et al., 2009). For some of its non-skeletal actions, including immunological effects, vitamin D may work together with calcium (Cantorna et al., 1999).

## **Doses of Vitamin D and Calcium**

The current Adequate Intake (AI), which is the amount that is thought to meet the daily needs of individuals, is 200–600 international units (IU) daily for vitamin D and 1,000–1,200 milligrams (mg) daily for calcium. The Tolerable Upper Intake Level (UL), which is the safe upper limit for regular use, is 2,000 IU daily for vitamin D and 2,500 mg for calcium (Jellin et al., 2009). Due to possible widespread public health issues that could be caused by the vitamin D deficiency epidemic, professional organizations, physicians, and scientists have proposed that the AI and UL of vitamin D should be raised significantly (Holick, 2008; Moyad, 2008; Ginde et al., 2009).

## **VITAMIN D DEFICIENCY: PREVALENCE AND CAUSES**

Vitamin D deficiency is now an epidemic in the United States and many other countries. It has been estimated that one billion people around the world have vitamin D insufficiency or deficiency.

## **Vitamin D Levels in the General Population**

Rigorous, epidemiologic studies of the US population, obtained through the NHANES (National Health and Nutrition Examination Survey), found that 77% of American adults had deficient or insufficient levels of vitamin D in 2004. In one study of American adults who had a reasonable intake of vitamin D (took a multivitamin daily and consumed salmon once weekly and milk daily), it was found that about one-third were vitamin D-deficient. Several studies indicate that 40–90% of American children, including newborns, have insufficient or deficient vitamin D levels (Ginde et al., 2009; Holick, 2007, 2008; Holick & Chen, 2008).

## **Causes of Vitamin D Deficiency**

Vitamin D deficiency has several causes, some of which relate to sun exposure and synthesis of vitamin D in the skin. Avoidance of sun exposure and the use of sunscreen and sun-protective clothing are among the more common causes. Sun exposure is also related to time of year and geographic location—with sun exposure being lower (and the risk of vitamin D deficiency higher) during winter months and in geographic areas that are farther from the equator. High skin pigmentation, especially among African-Americans, decreases sun-induced vitamin D synthesis in the skin and is therefore a risk factor for vitamin D deficiency. Other common causes for vitamin D deficiency include aging, obesity, and decreased dietary vitamin D intake (Holick, 2007, 2008; Moyad, 2008).

## **BIOLOGICAL EFFECTS OF VITAMIN D**

For years it has been known that vitamin D helps to regulate calcium absorption and to maintain bone health. More recent studies have found that vitamin D's actions on the body are much more widespread. In fact, most cells and tissues of the body have mechanisms for synthesizing and responding to vitamin D. Thus, vitamin D affects many organs and body processes and may thereby have important effects on general health and well-being (Holick, 2007, 2008). In the case of the immune system, studies over the past decade have shown that vitamin D has anti-inflammatory and immunoregulatory effects (Adorini & Penna, 2008; Smolders et al., 2008b; Szodoray et al., 2008).

## **VITAMIN D DEFICIENCY: ASSOCIATED MEDICAL CONDITIONS**

Vitamin D deficiency has been associated with many different diseases. It may increase the risk of bone fractures and cause osteopenia and osteoporosis (Holick, 2007, 2008). Inadequate vitamin D may cause myopathy, muscle weakness, and increased the risk of falls (Ceglia, 2008). Presumably through immunological effects, vitamin D deficiency has been associated with increased risk and increased disease severity in MS as well as other immune diseases, including type 1 diabetes, rheumatoid arthritis, and osteoarthritis. Vitamin D deficiency may also increase the risk for multiple forms of cancer, heart and lung diseases, depression, and schizophrenia (Holick, 2007; Holick & Chen, 2008).

## **VITAMIN D DEFICIENCY: POSSIBLE EFFECTS ON MS**

In MS, vitamin D may have preventative as well as disease-modifying effects. In EAE (experimental autoimmune encephalomyelitis), the animal model of MS, vitamin D supplementation prevents and slows the progression of the disease while vitamin D deficiency worsens the disease (Cantorna et al., 1996, 2000; Pedersen et al., 2007). The risk of developing MS appears to be lower in those with relatively high intakes or relatively high blood levels of vitamin D (Ascherio & Munger, 2007). In those with MS, high vitamin D levels have been associated with decreased risk for attacks and less severe disability (Smolders et al., 2008a; van der Mei, 2007).

## IMPLICATIONS FOR PEOPLE WITH MS

Due to the widespread effects of vitamin D, vitamin D deficiency may have several important implications for those with MS. The most definitive concern is bone health. People with MS are prone to osteoporosis. As a result, vitamin D deficiency could increase the risk for, or worsen, this condition and thereby increase the risk for fractures. Another MS-specific concern is that MS-associated weakness could be caused by, or worsened by, vitamin D deficiency. Finally, although the information at this point is not definitive, vitamin D deficiency could worsen the underlying disease process of MS.

In addition to having possible effects on those with MS, vitamin D may play a role in actually causing MS. Thus, adequate vitamin D levels could possibly prevent MS or cause MS to develop at a later age. This concept has important implications for trying to prevent MS in the general population and may be especially relevant to the children of people with MS, who, on a genetic basis, are known to have a mildly increased risk of developing the disease.

## COSTS

With the rising costs of health care, there are growing concerns about the costs of diagnostic tests and therapies. Approximate costs for diagnosing and treating vitamin D deficiency and related conditions are (Shi et al., 2009):

◆ Blood test for 25-hydroxyvitamin D:	\$50–200
◆ Vitamin D supplements (1,000–2,000 IU daily):	\$3–6/month
◆ Osteoporosis medications:	\$50–100/month
◆ alendronate sodium	
◆ ibandronate sodium	
◆ raloxifene HCl	
◆ risedronate sodium	
◆ Bone densitometry:	\$150–250
◆ Bone fractures (direct healthcare costs, first year)	
◆ Hip	\$15,000–25,000
◆ Vertebral	\$6,000–15,000
◆ Other	\$6,000–9,000

## WHAT TO DO IN CLINICAL PRACTICE?

Current research indicates that vitamin D may play an important role in MS. However, additional research needs to be done in this area. Specifically, there is a need for studies, especially large-scale clinical trials, to determine the exact effects of vitamin D supplementation on the disease process and the symptoms of MS. In the meantime, should clinicians check vitamin D levels or recommend vitamin D supplements? There are three general strategies that may be used in clinical practice:

- ◆ **Wait Until More Information Is Available** (do not check vitamin D levels or recommend vitamin D supplements)

This may be the most common approach at this time. This strategy may be actively chosen by those who want additional information before changing clinical practice. This approach may also be passively used, in a “default” manner, by clinicians who are not aware of vitamin D information and thus have not considered whether they want to incorporate vitamin D testing or supplementation into their clinical practice.

- ◆ **Advantages:** When actively chosen, this approach is based on waiting until absolutely definitive information is available. It is possible, though very unlikely, that future research will demonstrate that supplementation with vitamin D or calcium is harmful for people with MS. From a cost perspective, this strategy avoids the costs of the blood test (\$50–200) and supplements (\$3–6/month).
- ◆ **Disadvantages:** The concern with this approach is that the large number of people with MS who are vitamin D-deficient will not be diagnosed with vitamin D deficiency and thus will not receive, or obtain the potential benefits of, supplementation. Undiagnosed and untreated vitamin D deficiency could lead to osteoporosis, bone fractures, and other associated morbidity. Costs for diagnosing and treating osteoporosis-related conditions include bone densitometry (\$150–250), osteoporosis medications (\$50–100/month), and treatment for bone fractures (\$6,000–25,000). In addition to osteoporosis, it is possible that undiagnosed and untreated vitamin D deficiency could cause weakness, worsen the disease course of MS, and increase the risk for developing other vitamin D deficiency-associated conditions.

- ◆ **Supplement “Blindly”** (recommend vitamin D supplements without checking vitamin D levels)

With this approach, vitamin D levels are not obtained but a modest dose of vitamin D, such as 1,000 IU daily, is recommended.

- ◆ **Advantages:** For those who are vitamin D-deficient, this approach may provide benefits for bone health as well as strength, general health and, possibly, MS. This approach avoids the inconvenience and cost (\$50–200) of the blood test.
  - ◆ **Disadvantages:** For those who are not vitamin D-deficient, this approach will result in unnecessary supplementation—this supplementation has associated inconvenience and cost. For those who have deficiency that is not corrected with the “blind” supplementation, there will be a false sense of security and they will, unknowingly, still be at risk for various vitamin D deficiency-related conditions.
- ◆ **Supplement if Blood Levels Are Low** (check vitamin D levels and recommend vitamin D supplements if blood levels are low)

With this approach, blood levels of “25-hydroxyvitamin D” are obtained. If the level is normal, vitamin D supplements are not recommended. If the vitamin D level is low (below 35–40 ng/mL), then vitamin D supplements, as well as vitamin D-rich foods, are

recommended. After supplementing for three to six months, the blood level is rechecked to be certain that it is in the normal range. It may then be reasonable to check blood levels on a yearly basis (Cannell and Hollis, 2008; Moyad, 2008).

The optimal approaches for supplementing in the general population and in those with MS have not been established. General guidelines have been proposed (Cannell and Hollis, 2008; Holick, 2007; Moyad, 2008). The amount of supplementation that is needed varies between individual patients and depends on where one lives and the time of year. A general strategy that may be effective in many parts of the United States is 1,000 IU of vitamin D daily for levels between 20 and 35–40 ng/mL and 2,000 IU daily for levels below 20 ng/mL. In some regions, such as the Pacific Northwest, higher doses may be necessary: after initial treatment with 50,000 IU weekly for two months, maintenance dosing with 2,000–5,000 IU daily or 50,000 IU every two weeks may be needed. As noted, the official standards, which are controversial (Holick 2008; Moyad 2008; Ginde et al, 2009), state that the tolerable upper intake level (UL), which is the safe upper limit for regular use, is 2,000 IU daily for vitamin D. Vitamin D3 supplements, which are about the same price as vitamin D2 supplements, appear to be preferable because, relative to vitamin D2, vitamin D3 is more active biologically, raises blood levels more effectively, and is more stable on the shelf (Cannell and Hollis, 2008; Holick, 2007; Moyad, 2008). Calcium supplements are often taken with vitamin D. Daily doses of 1,000–1,200 mg of calcium are generally recommended (Jellin, 2009).

Importantly, these strategies for diagnosing and treating vitamin D deficiency are “best guesses” based on current evidence. Ongoing research in this area may, in the future, lead to more formal protocols, changes in the “normal” blood level ranges for 25-hydroxyvitamin D, and changes in the recommended daily amounts and tolerable upper intake levels for vitamin D. In addition, further research may lead to MS-specific guidelines for optimal blood levels and supplementation strategies.

- ◆ **Advantages:** For those who are not vitamin D-deficient, this approach avoids unnecessary supplementation. For those who are found to be vitamin D-deficient, this strategy may improve bone health and, additionally, could increase muscle strength, slow the disease course of MS, and improve general health. Through prevention, this approach may avoid the costs of bone densitometry (\$150–250) and osteoporosis medications (\$50–100/month), and the costs (\$6,000–25,000) and morbidity of bone fractures. This approach may also avoid the costs and adverse health effects associated with developing other vitamin D deficiency-associated diseases, such as other immune diseases and cancers.
- ◆ **Disadvantages:** This approach relies on vitamin D information that is not absolutely complete—as a result, it is conceivable, although very unlikely, that additional research will identify concerns about the safety or effectiveness of treating vitamin D deficiency in those with MS. Also, this strategy incurs costs for the blood test (\$50–200), and, if indicated, vitamin D supplements (\$3–6/month).



Clinicians who treat people with MS should become familiar with current vitamin D information so that they are able to educate their patients, and, if appropriate, diagnose and treat vitamin D deficiency. Also, due to the inherited risk of MS and the possible preventative effect of vitamin D supplementation, it may be reasonable for clinicians to discuss the possible implications of vitamin D deficiency and supplementation for the children of those with MS.

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