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Andrew J. Solomon, MD

WHAT IS VITAMIN D AND WHY IS IT IMPORTANT

IN MS? Vitamin D is a vitamin that acts like a hormone in the human body. We get vitamin D from sunlight, food, or dietary supplements. The study by Stein et al.¹ examines the relationship of vitamin D and MS. In addition, a recent Patient Page in *Neurology*[®] focused on the actions of vitamin D and vitamin D deficiency.² The best level of vitamin D for health is uncertain and may vary depending on the part of the body vitamin D acts on. Many experts believe that blood levels of vitamin D above 30 ng/mL are adequate. (Some studies, such as the present study, use different units of measurement [nmol/L] than are common in the United States. A conversion factor of 2.496 is necessary to switch between these unit systems, and a vitamin D level of 30 ng/mL would be approximately 75 nmol/L in the present study.¹)

Vitamin D appears to act on a number of different systems in the human body. In particular, vitamin D seems to be important for function of the immune system. Therefore, deficiency of vitamin D may play a role in diseases thought to be caused by improper immune responses (autoimmune diseases), including multiple sclerosis (MS). A recent Patient Page in *Neurology* provided a thoughtful summary of what is known about MS.³

Previous studies have found that low vitamin D levels may increase the risk of developing MS.^{4–8} A number of studies have also suggested that patients with MS with low levels of vitamin D are at an increased risk of new MS attacks (“relapses”), new lesions on MRI, and disability compared to patients with higher vitamin D levels.^{4–8} These studies mostly looked at a connection with previous and current vitamin D levels, rather than at the effect of supplementing vitamin D. Most found that patients with MS appeared to benefit from having adequate vitamin D levels (i.e., approximately 30 ng/mL) compared to insufficiency (20–29 ng/mL) or deficiency (less than 20 ng/mL). A few studies also suggested that levels higher than 30 ng/mL may further help protect patients with MS.

WHAT DID THE AUTHORS STUDY? In the present study, Stein et al.¹ examined whether high vita-

min D levels produced by vitamin supplementation were better than adequate vitamin D levels in patients with MS. The study included patients with “active” relapsing-remitting MS as defined by a relapse within the last 24 months.

Half the participants were assigned to a “low-dose” vitamin D group and half to a “high-dose” group. The aim of the study was to reach blood levels of vitamin D of 52–70 ng/mL in the high-dose group and compare its effect on MS to the low-dose group with adequate (i.e., about 30 ng/mL) levels. Every participant received 1,000 IU vitamin D₂, a synthetic form of vitamin D derived from plants. The low-dose group received an additional pill that was placebo (a “sugar pill”). The high-dose group received an identical pill containing 6,000 IU of additional vitamin D₂. Vitamin D levels were checked during the study and capsules were changed to achieve the goal vitamin D levels. When a high-dose group member had the second capsule adjusted, a low-dose group member had a placebo capsule changed at the same time. This was done so none of the participants would know which group they were in.

The authors hoped to see if participants with high vitamin D levels had fewer new lesions or changes on their MRI suggestive of disease activity, fewer relapses, and less disability, at the end of 6 months, compared to participants with simply adequate levels of vitamin D. Twenty-three patients with MS participated in the study.

WHY IS THIS STUDY IMPORTANT? This study is the first published randomized double-blind placebo-controlled trial of vitamin D supplementation in patients with MS. Randomized controlled trials (RCT) are considered to produce the most reliable scientific data. They attempt to evenly sort patients to the treatment and placebo group so that no factors other than the treatment under study affect the results. They are less likely to be affected by “bias” and are the best way to show that a treatment caused a particular effect. The study was also designed so that the authors and patients were both “blinded” to which patients were in the high-dose vitamin D and which were in the placebo group.

Previous studies on vitamin D in MS did not have such a strong study design. They were more susceptible to bias, and this has limited the strength of the conclusions from these studies. RCT have been needed to confirm the association between vitamin D and MS suggested by these previous studies and to determine if vitamin D supplementation may help patients with MS.

WHAT WERE THE RESULTS? With supplementation, the median vitamin D level in the low-dose group rose from 22 ng/dL to 28 ng/dL at the end of the study. The median vitamin D level in the high-dose group rose from 24 ng/mL to 48 ng/mL. While the high-dose group did reach higher levels of vitamin D, there were no significant differences between the groups in regard to MRI changes. The high-dose group actually had significantly more relapses and worse disability than the low-dose group at the end of the study. Thus in this study, there seemed to be no advantage from high-dose vitamin D supplementation in patients with MS compared to supplementation for adequate vitamin D levels.

WHAT DOES THIS MEAN FOR PATIENTS WITH MS AND WHAT FURTHER RESEARCH IS NEEDED? Research suggests that adequate vitamin D levels, compared to insufficiency or deficiency, may protect against the development of MS and prevent disease activity and disability in patients diagnosed with MS. Although this study did not find that high vitamin D levels were more protective for patients with MS than adequate levels, several characteristics of the study may have affected this finding. The small size and short length of the study may have made it difficult to find a difference between the groups. A study with a larger number of patients followed over the course of 1–2 years may have detected a benefit from high-dose vitamin D.

A number of patients with less active or different forms of MS, more severe disability, and taking certain medications for MS were excluded from this study. It remains unknown if higher vitamin D levels may have benefit for these patients. There are also different forms of vitamin D supplements. It is uncertain if these different forms are equal and act in the same way in the body. It is also possible that a

higher vitamin D level than was achieved by this study was needed to see a benefit. Although the vitamin D levels in the 2 groups were different at the end of the study, there were some individuals in each group who had similar vitamin D levels. Since the number of participants was small, this may have weakened any effect of high-dose vitamin D on MS disease activity.

This study also found that there were more relapses and disability in the high vitamin D dose group. This is different from the results of previous studies. Much of this effect might have come from one participant in the high-dose group with very active MS. If the data from this single participant were removed, no difference was then seen between relapse rate and disability between the groups. It is not clear that high-dose vitamin D is worse for patients with MS. These results need to be confirmed by further study.

More research is needed to determine the best level of vitamin D for patients with MS. Several additional studies are underway now. While we wait for these results, research so far suggests that it may be beneficial for patients with MS with vitamin D insufficiency or deficiency to take vitamin D supplementation for a goal level of greater than 30 ng/mL.

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