A vitamin D-efense against multiple sclerosis

Safety and immunologic effects of high- vs low-dose cholecalciferol in multiple sclerosis

Introduction

Multiple sclerosis (MS) is the most prevalent immune-mediated disease affecting the central nervous system (CNS). The CNS is made up of the brain and spinal cord, which are responsible for controlling the functions of your body. The precise causes of MS are currently unknown.

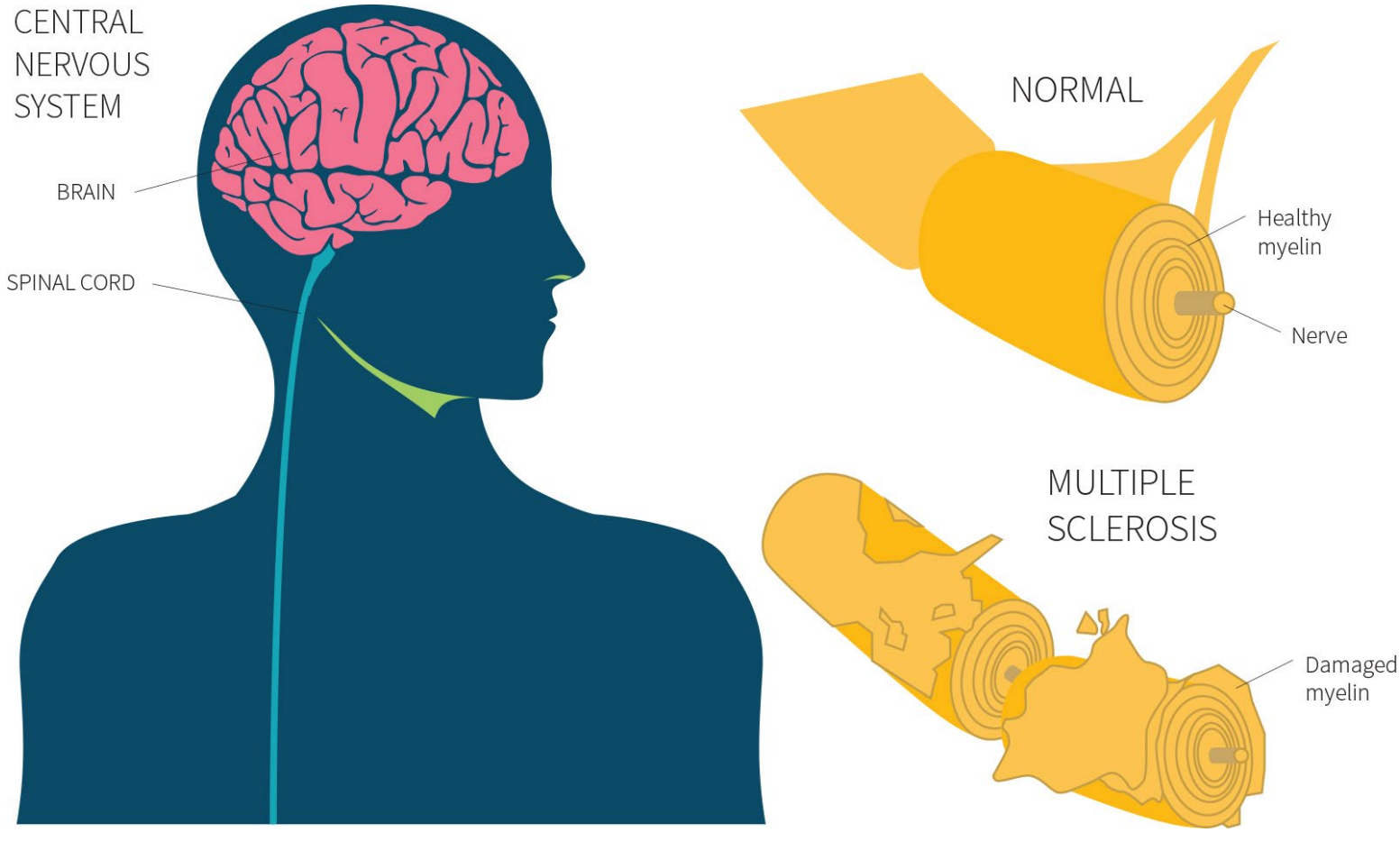
However, it is well-established that the effects of MS involve a degradation of the nerves of the brain and spinal cord (as seen in Figure 1). These nerves transport electrical signals all around your body, allowing for activities like voluntary movement. Nerves are insulated by the myelin sheath, which protects the signal quality of these electrical transmissions. With MS, the myelin insulation is damaged, affecting the ability of nerve cells to effectively communicate. In addition to affecting movement patterns, MS also impairs cognitive ability, a symptom that worsens as the disease progresses over years.

Many immunologic, genetic, and environmental variables have been implicated in the pathology of MS. One variable examined has been the connection between the risk of MS and vitamin D levels. Some studies have shown that decreases in MS related relapses are associated with higher vitamin D levels. The underlying mechanism is not entirely understood, but one hypothesis about this relationship is that vitamin D is able to modify or help regulate certain aspects of the immune system, such as inflammatory T cells, that have been linked to the development of MS.

However, questions still remain about what a safe dose of vitamin D may be and what role this vitamin may play in the immune system. The study under review investigates the safety and immunologic effects of a high versus low dose of vitamin D in patients with MS.

Multiple sclerosis (MS) is thought to have an immune system-mediated component to its development. Factors such as vitamin D status may play a role in its prevalence due, in part, to vitamin D's interactions with the immune system. The current study investigates the effects a high or low dose of vitamin D has on immune functions of people with MS.

Figure 1: How MS damages your nerves



Who and what was studied?

Researchers randomized 19 men and women with a diagnosis of relapsing-remitting MS (RRMS), ages 18 to 55, into the high-dose vitamin D group, and 21 participants were randomized into the low-dose group. RRMS is the most common MS diagnosis, characterized by generally infrequent attacks with long periods of little or no disease progression.

All participants had serum vitamin D levels of 20 to 50 nanograms per milliliter, placing them into the vitamin D "adequate" category as defined by the Institute of Medicine. The high-dose group received 10,000 IU and the low-dose 400 IU of cholecalciferol (vitamin D3) every day for six months. For reference, the recommended dietary allowances for adult men and women is 600 IU a day. In addition to the vitamin D3 supplement, all participants received a daily multivitamin that included 400 additional IU of D3 and 1,000 milligrams of calcium, bringing the vitamin D intervention totals to 10,400 and 800 IU daily. Both the participants and the researchers were blinded to the treatment assignments. Bloodwork was taken at baseline, three months, and six months.

The primary outcomes in this study were the changes in two components of the immune system: interferon-γ (IFN-γ) and interleukin-17 (IL-17). Both of these are types of cytokines, proteins that are involved in cell signaling. Interferon-γ plays a role in immunity against pathogens and in tumor control while interleukin-17 helps to mediate pro-inflammatory responses. In particular, IL-17 immune activation has been associated with MS-induced brain lesions. Measurements for these cytokines were taken using blood samples from the participants. The frequency of adverse events was also tracked between the two groups to help assess the safety of the vitamin D3 doses being used.

Forty participants were randomized into either a high-dose vitamin D group receiving a total of 10,400 IU a day or a low-dose group receiving 800 IU a day. Changes in interferon-γ (IFN-γ) and interleukin-17 (IL-17), components of the immune system, were measured at baseline, three months, and six months. Adverse events were noted to help establish dosage safety for vitamin D.

What were the findings?

Thirty-five patients completed the study. Only two MS relapses occurred during the study period, one in each research group. Both patients were able to complete the study. Some participants in both groups experienced nausea, which stopped after supplementation was discontinued. It is not clear if this was related to the vitamin D. Serum vitamin D levels increased significantly more in the high-dose group (+34.9 nanograms per milliliter) than in the low-dose group (6.9 nanograms per milliliter).

In the high-dose group, IL-17 levels were substantially decreased between baseline and the six-month mark. A similar reduction was not observed in the low-dose group. Greater reductions in IFN-γ were also seen in the high-dose group, but these changes were not significantly different from the low-dose intervention. The decreases seen in IL-17 correlated with the increases seen in vitamin D levels. When the serum increase of vitamin D was greater than 18 nanograms per milliliter, every five nanograms per milliliter increase above that threshold saw a 1% absolute decrease in the percentage of IL-17 cells observed.

Cytokines and your immune system

Cytokines are small proteins that communicate immune-related information locally between cells. They kind of act like the "hormones" of the immune system. Some are pro-inflammatory while others are anti-inflammatory. Their primary purpose is to initiate, carry out, and then cease immune system responses that are appropriate to the situation. An immune response to a repair a cut on your hand will differ from that of fighting off a viral infection. Cytokines help direct the immune system components to appropriately respond to these varying scenarios.

Certain supplements, such as turmeric, can have anti-inflammatory effects that act by suppressing the production of pro-inflammatory cytokines. In the case of MS, a particular cytokine, IL-17, becomes upregulated. IL-17's pro-inflammatory properties have been associated with the active lesions seen in brains of patients with MS. This association is why therapies helping to downregulate IL-17's production may aid in slowing the progress of MS.

High-dose vitamin D was able to lower IL-17 and IFN-γ, although only the decreases in IL-17 were statistically significant. The low-dose was ineffective at lowering either. Decreases with IL-17 were correlated with the increases in serum vitamin D, with a 1% absolute decrease in the percentage of IL-17 occurring for every 18 ng/mL increase in serum vitamin D. No serious adverse effects were seen at any dose, and the rates of relapse in each group were similar.

What does the study really tell us?

This study demonstrated that high daily doses of D_3 at 10,400 IU can be safe and well-tolerated by people with MS. The researchers have shown that this high dose can help modulate immune system factors that may exacerbate the progression of MS. An optimal level of vitamin D for people with MS is not currently known. Preferred levels may differ for people with MS, compared to the general public. Researchers in this trial suggest that a level between 40 and 60 nanograms per milliliter may be an optimal range.

One area this study did not evaluate was clinical outcomes or changes in MS progression. However, there are trials in the works that are looking to answer that question using vitamin D supplementation dosages ranging from 5,000 to 20,000 IU. Vitamin D may prove to be a viable therapeutic option that could be given concurrently with primary MS medications. However, it is not yet known if the reductions in IL-17 and IFN-γ seen in this trial will yield clinically relevant results. While high doses of vitamin D are able to bring about these reductions, they may not be all that important if these effects are not biologically meaningful.

One limitations of the study was the exclusion of patients with vitamin D deficiency, defined within the study as less than 20 nanograms per milliliter. In theory, these participants would have been expected to experience the most improvement in response to supplementation, but the researchers felt it would not have been ethical to withhold effective treatment for these people for the six-month study duration had they ended up in the low-dose group.

Another limitation was the variety of immunomodulatory medications the patients were on. While this did not differ between groups, it is possible that some of these medications modified the treatment effect. This may be good news for future clinical applications, but it makes it hard to ascertain the degree to which vitamin D had an effect.

A high daily dose of vitamin D_3 of 10,400 IU appears to be safe for patients with MS. Studies are currently underway that will help shed light on what the clinical implications of a vitamin D treatment might mean for slowing the progression of MS or preventing relapses. Potential limitations were the exclusion of people with very low vitamin D, and medications the patients were on that may have impacted some of the results.

The big picture

Currently, there is no known cure or proven treatment for slowing the progression of this disease. Figure 2 shows an example of progressive brain effects from having MS. In the US, there are 12 approved medications that may help to reduce the frequency of relapses, but their ability to affect long-term disability is unclear. Life expectancy in patients with MS can be reduced by 7 to 14 years. A cheap secondary therapy like vitamin D, if proven effective, would be a welcome addition to the potential treatments options doctors and patients can use to manage MS.

Some studies have even hinted at a synergistic effect between vitamin D and INF-β, one of the first treatments developed to help prevent relapses. One study examining this relationship found that INF-β was associated with reduced relapse risk if vitamin D levels were at 20 nanograms per milliliter or greater. Those that fell below this level were at increased risk of relapse. Larger trials will be needed to help determine the exact interactions between INF-β and vitamin D, and if there might be any negative side effects when large doses of vitamin D are used over longer periods of time.

Twelve medications have been approved for the treatment of MS by the FDA, but their ability to improve long-term disability is unclear. Vitamin D, if shown to be effective, could be a cheap secondary therapy that may have some synergistic effects with current MS treatments.

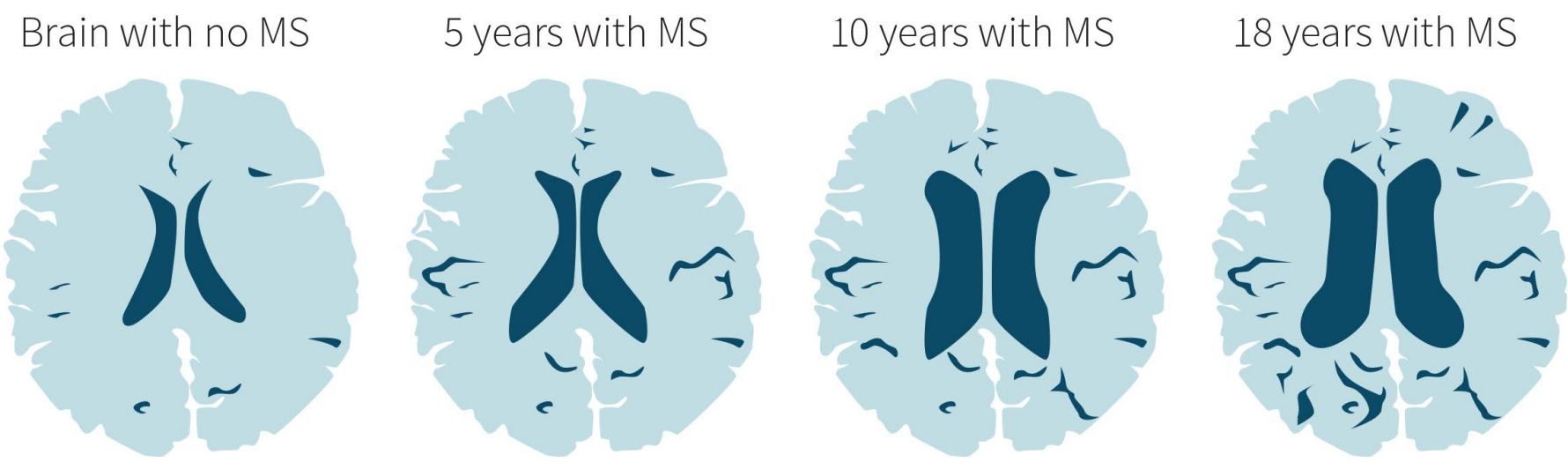
Frequently asked questions

Would a vitamin D treatment be viable for all types of MS?

There are three general disease patterns that may classify as MS phenotypes. Upon initial onset of the disease, the majority of patients will be classified as relapsing-remitting multiple sclerosis (RRMS). Disease progression between periods of relapse is usually minimal, although the attacks themselves can cause a patient to become more disabled.

Secondary progressive multiple sclerosis is usually seen as an initial RRMS diagnosis, but unlike RRMS, these

Figure 2:- Effect of MS on the brain



Reference: Bermel et al. Lancet Neurol. 2006 Feb.

patients will see a gradual worsening of symptoms (some of which are shown in Figure 3) with or without relapses. Lastly, primary progressive multiple sclerosis is a steady increase in disability from disease onset and has the worst prognosis. This accounts for about 10% of MS cases from initial diagnosis. While vitamin D supplementation may be a viable treatment option for all of these MS subtypes, the efficacy is not well understood. Presently, current and pending trials are primarily looking at patients with RRMS, as it is the most common diagnosis.

Are there any potential concerns with taking high doses of vitamin D for extended periods?

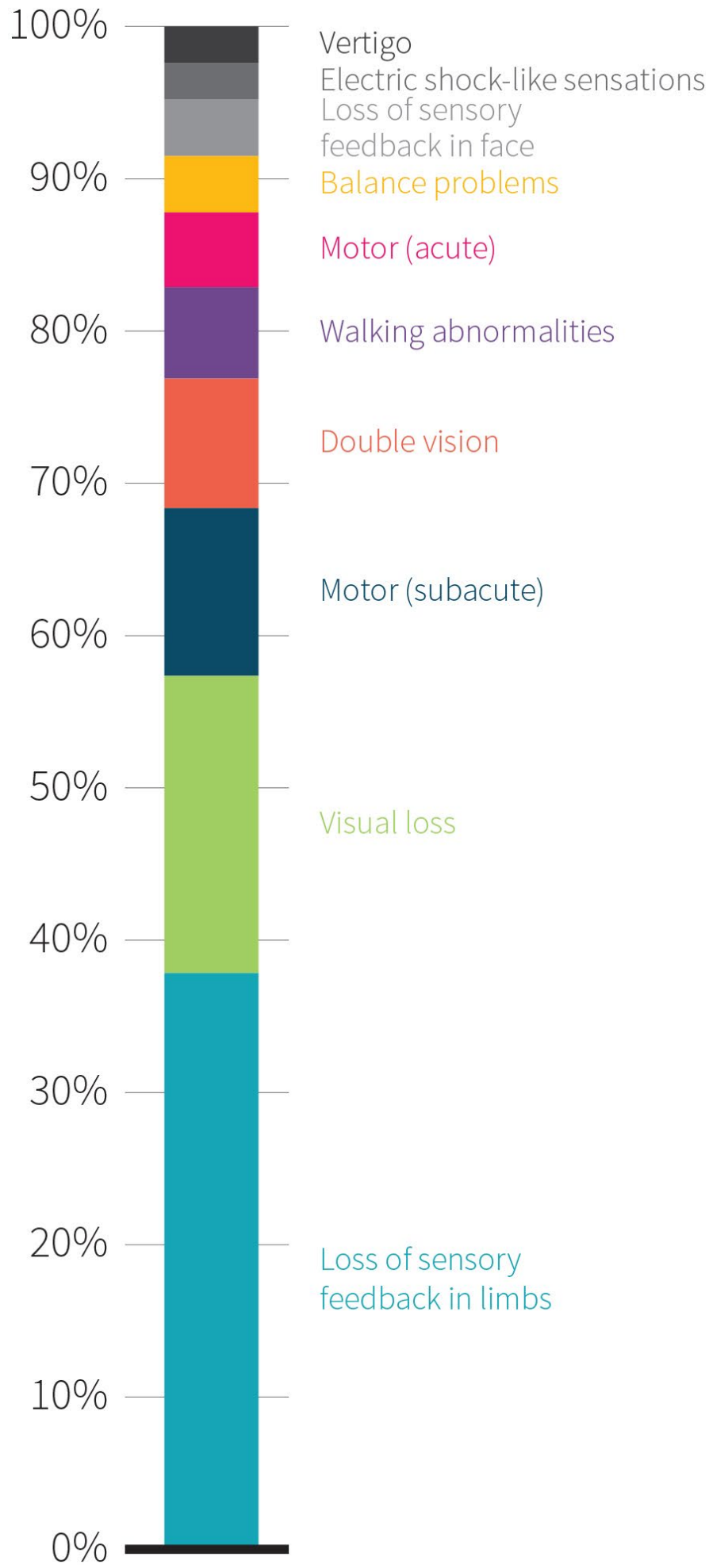
Vitamin D is relatively non-toxic but large doses can put the user at risk for hypercalcemia, where too much calcium is absorbed and deposited in the blood stream. However, it does appear to be safe to consume up to 10,000 IU a day with no visible signs or symptoms associated with vitamin D toxicity.

That being said, one study on elderly patients also covered in this volume of the ERD did see an increase risk of falls with high-dose vitamin D taken once monthly. But once-a-month high doses are not needed for most people. For the majority of those looking to supplement, a daily intake between 1,000 to 2,000 IU a day should suffice, although a 5,000 IU daily dose is not uncommon for people with particularly low levels.

Is there any way to know if I'm genetically susceptible to MS? If I am, should I take vitamin D preventatively?

While more than 100 genes have been associated with MS, it is hard to say just how predictive these markers are without taking into account environmental and lifestyle variables. Someone carrying the genes associated with increased risk of MS may never develop the disease. At present, alterations in the HLA-DRB1 gene have shown the strongest associated genetic risk factors for MS. HLA-DRB1 genes play a role in the immune system, which may help to explain why the pathology of the disease is closely tied to dysfunction

Figure 3: Symptom prevalence in MS



Reference: Richards et al. Health Technol Assess. 2002.

certain immune system components like interleukin-17. Currently, there are projects in the works that are hoping to develop systems for predicting MS risk, but at present no reliable tests are available. Furthermore, ensuring that you have adequate vitamin D levels is always a good idea, but there is no conclusive evidence that it can decrease your risk of developing MS.

What should I know?

This trial has provided us with important information about the relationship between vitamin D and MS. Primarily, that high doses of vitamin D up to 10,400 IU a day can be safe and that it does seem to modulate aspects of the immune system associated with MS. However, it is not yet known if these results are clinically relevant. Trials are currently in the works that will progress this line of research and will help to inform us about what, if any, clinical applications a vitamin D supplement may have as an immunomodulatory MS treatment option. ◆

Vitamin D is publically associated with bone health, but immune health may be an even bigger factor. Discuss all things vitamin D at the ERD Facebook forum.