ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Vitamin D Deficiency and Supplementation in Patients with IBD

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G&H How prevalent is vitamin D deficiency in the United States, and what accounts for it?

HP It should be understood that vitamin D is a pleiotropic hormone, rather than a vitamin. As a hormone, it has actions on the immune system, brain, muscles, and a number of other systems. Traditionally, for lack of knowledge about the specific effects of vitamin D on other organ systems, sufficiency of this vitamin has been defined by its effects on bone. The vitamin D status of a person is evaluated via its biomarker, the serum 25-hydroxyvitamin D concentration. The Institute of Medicine and the American Academy of Pediatrics have endorsed the serum concentration of 20 ng/mL—or 50 nmol/L—as the minimum level of vitamin D sufficiency simply because concentrations lower than this have been associated with rickets. However, many experts have endorsed a serum 25-hydroxyvitamin D concentration of 32 ng/mL as the level of sufficiency in older adults based on the maximal suppression of parathyroid hormone, which is achieved by this level of vitamin D.

As for the prevalence of vitamin D deficiency, defined as a serum 25-hydroxyvitamin D concentration below 20 ng/mL, good information comes from the National Health and Nutrition Examination Survey (NHANES), which has been monitoring dietary intake and nutrient levels of thousands of Americans since 1988. According to NHANES, about 30% of Americans, including children, are vitamin D–deficient. Another study of healthy adolescents in the northern-latitude city of Boston found a prevalence of vitamin D deficiency of about 42%.

But what accounts for vitamin D deficiency? Vitamin D levels in the human body depend on sun exposure, skin pigmentation, oral intake of the vitamin, its absorption from the intestines, and its distribution in the body, with the knowledge that the vitamin is sequestered in fat tissue. Several studies have found that vitamin D levels are lower in the winter, probably because of lack of sun exposure; lower in persons with darker skin complexion, although the reason for this is unknown; lower in persons who do not take supplemental vitamin D; and lower in persons with chronic illnesses and in those who are overweight.

G&H What accounts for suboptimal serum vitamin D levels specifically in persons with inflammatory bowel disease?

HP In addition to the factors that contribute to low vitamin D levels in healthy persons, several other factors affect the vitamin D status of persons with inflammatory bowel disease (IBD). Although there are no definitive studies on this, persons with IBD may spend less time outdoors and, therefore, have more limited sun exposure than healthy persons, and they also may have a decreased oral intake of vitamin D, considering that many limit consumption of dairy products. An important factor that contributes to vitamin D deficiency in persons with IBD may be intestinal inflammation, which may compromise absorption of vitamin D in the small intestine. Inflammation of the intestine could also result in leakage of vitamin D from the intestinal lumen. In fact, studies have linked lower vitamin D levels in patients with IBD to

more severe disease, upper gastrointestinal involvement, and especially Crohn's disease.

As for differences regarding vitamin D status between adults and children with IBD, no head-to-head comparison studies have been done. According to studies of the vitamin D status of patients with IBD performed so far, up to 40% of affected adults and children have vitamin D levels that are less than 20 ng/mL.

G&H What is the impact of vitamin D deficiency on the development and course of IBD?

HP Vitamin D, which I already mentioned is a unique nutrient that acts as a hormone, exerts its activity by binding to cellular vitamin D receptors. Cells of the immune system, especially those of the intestines, are among the cell lines that have the most abundant vitamin D receptors. Investigators studying the impact of vitamin D on the immune system have found that vitamin D plays a role in the normal functioning of all 3 tiers of the immune system's response against pathogens. The first tier involves keeping intact the epithelial barrier, which is disrupted in patients with IBD, allowing exposure to pathogens. The second tier is innate immunity in which vitamin D induces the production of antibacterial enzymes, which kill invading pathogens once they are ingested by macrophages. Recent research has shown that this step of the immune system response is also disrupted in patients with IBD. The third tier is immune tolerance, which is disrupted in IBD. Vitamin D's role here is maintaining immune tolerance and reducing the production of cytokines, such as tumor necrosis factor (TNF) α. Therefore, it seems that vitamin D may counteract many immune system disruptions that occur in IBD.

As proof of the relationship between vitamin D status and development of IBD, epidemiologic studies report that the incidence of IBD is higher in northern latitudes than southern latitudes, thus associating lower vitamin D levels with higher incidence of IBD. However, this association could be confounded by genetic differences. A recent prospective cohort study of about 73,000 women followed for 22 years through the Nurses' Health Study found a significant reduction in the risk of development of Crohn's disease as well as a trend toward reduction in the risk of development of ulcerative colitis over time in women who had higher vitamin D levels at the inception of the study.

G&H What do we know about vitamin D supplementation as treatment for IBD?

HP The idea that vitamin D could be used as a therapeutic agent or an adjunct in the treatment of IBD is attractive. A few cross-sectional studies have noted an association between vitamin D status and severity of IBD, but the interpretation of these studies is controversial because low vitamin D levels could be the result, rather than the cause, of disease. Only 1 clinical trial has been conducted so far whereby patients with Crohn's disease were assigned to receive either placebo or 1200 international units of vitamin D. Fewer relapses were reported in those patients who received vitamin D supplementation. Clearly, more clinical trials of vitamin D in the treatment of IBD are warranted.

G&H Do genetics play a role in relation to vitamin D deficiency and risk of IBD development?

HP Vitamin D exerts its actions through the vitamin D receptor on cells, and it is well known that there are polymorphisms of the vitamin D receptor gene. Some of these polymorphisms may not result in lower vitamin D levels but may make the receptor less active when bound to vitamin D, and so some of the downstream effects of the vitamin may be attenuated. Higher levels of circulating vitamin D could compensate for a relatively defective vitamin D receptor, so vitamin D deficiency could result in more pronounced lack of vitamin D effects.

The vitamin D receptor gene is located on chromosome 12 very near the region where the most important candidate genes for IBD are located. Given the importance of vitamin D for the immune system, investigators have examined whether there is an association between any of the vitamin D receptor polymorphisms and IBD. A meta-analysis of existing studies on this topic found an association between certain polymorphisms and the risk of IBD development.

In addition, direct evidence from animal studies shows that vitamin D supplementation prevents or ameliorates the development of IBD in mice that are genetically manipulated to be at high risk for development of IBD. Large prospective studies in humans are needed to uncover any potential of vitamin D supplementation to reduce the risk of developing IBD in persons with a genetic predisposition to IBD development.

G&H What important clinical points were revealed in your studies on vitamin D supplementation in children and adolescents with IBD?

HP In our studies, we observed that the prevalence of vitamin D deficiency is high among children with IBD, both Crohn's disease and ulcerative colitis. We also observed variation in the prevalence of vitamin D deficiency in this population depending on the assay used, which highlights the importance of methodology in assessing vitamin D status. Most importantly, we found that the conventional treatment regimen of 2000 units of daily vitamin D for 6 to 8 weeks was not efficient in treating vitamin D deficiency in all deficient patients. A dose of 50,000 units per

week for 8 to 9 weeks, however, would be sufficient to correct the deficiency. We also surprisingly found lower levels of inflammatory markers and cytokines in children who received 2000 units of vitamin D per day than in children who received a lower daily dose of vitamin D supplementation for 1 year—findings that have recently been submitted for publication. This is among the first prospective studies to look at the effects of long-term vitamin D supplementation in pediatric patients with IBD. Additional studies are needed to confirm the association between vitamin D supplementation and amelioration of IBD and establish its mechanism of action.

G&H What are your thoughts on the potential use of vitamin D supplementation to boost anti-TNF therapy?

HP I mentioned that decreasing the production of TNF-α is a well-established action of vitamin D. Based on this action, vitamin D could be studied as a therapeutic agent in IBD and also as an adjunctive regimen in patients receiving anti-TNF therapy. A retrospective study has shown that patients with IBD and high vitamin D levels prior to starting an anti-TNF therapy regimen had a longer lasting response to the anti-TNF agent than patients with low vitamin D levels. This was a small clinical study and did not explore the mechanism of action of vitamin D. Large prospective trials, conducted in conjunction with translational studies, are needed to prove this potential role of vitamin D.

G&H What additional studies are needed in relation to the role of vitamin D and other nutrients in the pathogenesis of IBD?

HP Patients with IBD are prone to micronutrient deficiencies, such as deficiencies in folic acid, vitamin B12, and iron, in addition to vitamin D. Deficiencies may be caused by inflammation-associated small intestine malabsorption of these nutrients but also bowel resection in some patients. Only vitamin D has been specifically linked to the pathogenesis and risk of IBD so far, due to its effects on the immune system.

That said, nutrigenetics and nutrigenomics, 2 scientific fields that are in their infancy, are systematically examining the effect of nutrition on disease. Nutrigenetics examines the role of genes in our response to nutrients, and nutrigenomics examines the role of nutrients in the expression of genes. Nutrigenetic studies related to IBD could focus on how vitamin D receptor polymorphisms affect the pathogenesis and course of IBD. Nutrigenomic studies—which are currently being conducted—focus on the potential of folate, vitamin B12, vitamin E, and biotin to change the course or even prevent the development of intestinal inflammation by altering gene expression through methylation and histone differentiation.

G&H What advice do you have for clinicians regarding vitamin D deficiency and supplementation in patients with IBD?

HP Our current knowledge only allows for limited recommendations. I would advise physicians treating patients with IBD to anticipate vitamin D deficiency (25OHD <20 ng/mL) and monitor the vitamin D status of their patients, especially in patients with severe disease, patients with darker skin complexion, and patients who are either malnourished or overweight. The optimal timing for measurement of the surrogate marker—25-hydroxyvitamin D—in patients living in the northeastern United States is when the level is at its nadir, which usually occurs in late winter or early spring. If vitamin D deficiency is found, supplementation—or an increase in dosage of vitamin D if the patient is already taking a supplement—is recommended. Our study, conducted in adolescents and young adults, supports the use of a cumulative dose of vitamin D of about 400,000 to 450,000 units over 8 to 9 weeks, and we found that compliance is best if doses are delivered weekly.

Finally, maintenance vitamin D dosages have not been established in this population, but the latest study we conducted, which is going to be published shortly, suggests that dosages of up to 2000 units of vitamin D per day are safe, although they may not be adequate to maintain an optimal level of vitamin D (>30 ng/mL) in persons with IBD living in the northeast United States.

Dr Pappa has no relevant conflicts of interest to disclose.

Suggested Reading

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