ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Vitamin D and Inflammatory Bowel Disease

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G&H How common is vitamin D deficiency in patients with inflammatory bowel disease?

AA Normal levels of vitamin D are approximately 30 ng/mL. Levels between 20 and 30 ng/mL are considered insufficient, and anything below 20 ng/mL is considered deficient. The prevalence of vitamin D deficiency in inflammatory bowel disease (IBD) varies in different studies, but it appears that, at least in some studies, up to 60% to 70% of people with IBD have insufficient vitamin D levels. Of these, more than half meet the threshold for deficiency, and the remainder have levels consistent with vitamin D insufficiency. However, these numbers depend upon various factors, such as the location of the study, the season of measurement, and the proportion of people who have active disease.

G&H Which seems to come first: vitamin D deficiency or IBD?

AA This question comes up very frequently and is an important chicken-or-the-egg–type dilemma. Prospective data, including studies conducted by my colleagues and I, have suggested that low vitamin D levels may precede the diagnosis of IBD. In one study, women who had low levels of vitamin D had an increased risk of developing Crohn's disease over the subsequent 2 decades. Thus, while active IBD has been associated with low vitamin D levels, it does not appear that having a diagnosis of IBD entirely explains the prevalence of vitamin D deficiency seen in this cohort. Other studies have looked at people with a relatively new diagnosis of IBD, who have had symptoms for comparatively short durations of time, and have found a high prevalence of low vitamin D levels. Laboratory experiments in various mice models have also shown that animals are more susceptible to colitis and that such colitis can be treated by vitamin D supplementation. These findings suggest, in my opinion, that there is at least a significant component of vitamin D deficiency perhaps contributing to the development of IBD; vitamin D deficiency is not purely a consequence of prolonged, undertreated IBD or bowel damage.

However, it should be noted that as people have more active disease and have a longer duration of IBD, several factors—including reduction in physical activity, alteration in diet, and changes in the intestinal absorption of vitamin D—can contribute to making patients more susceptible to vitamin D deficiency as a consequence of IBD. Therefore, I believe that there is likely a bidirectional relationship in which IBD and its consequences can cause a patient to have low levels of vitamin D, and in which having a low vitamin D level itself can affect a patient's immune response and predispose the patient to having IBD or having a relapse of his or her IBD.

G&H Is vitamin D deficiency more common in Crohn's disease than in ulcerative colitis?

AA The data are not very clear on this issue. Certainly, more associations have been described between vitamin D and Crohn's disease than with ulcerative colitis, so there does seem to be a link favoring Crohn's disease in terms of pathogenesis and relapse. However, there does also seem to be an association between ulcerative colitis disease activity and vitamin D. Several studies have shown that vitamin D levels are low in people with ulcerative colitis and in those with Crohn's disease who do not have much small bowel involvement.

G&H How does vitamin D affect the severity of IBD or its complications?

AA A growing body of literature has linked disease severity to low vitamin D levels. For example, my colleagues and I looked at a cohort of nearly 3000 people with Crohn's disease or ulcerative colitis and examined vitamin D levels and future risk of surgery and hospitalizations. We were able to show that there clearly is a gradation in the risk of surgery in people who had normal, insufficient, and deficient levels of vitamin D. People who had insufficient levels of vitamin D (20-30 ng/mL) had a higher risk of surgery and hospitalization, and people with levels lower than 20 ng/mL had an even higher risk of surgery and hospitalization. Other studies have similarly shown that people with higher disease activity tend to be low in vitamin D, and the risk of surgery and hospitalization tends to be higher in those who are deficient compared to those who are not, suggesting a link between vitamin D levels and the risk of surgery and hospitalization.

My colleagues and I have also performed studies showing that low vitamin D levels may have an influence on IBD, not just through an effect on disease activity but on other complications as well. Vitamin D can be considered a hormone with a number of effects on the immune system that are responsible for mediating susceptibility to infections and perhaps malignancy. Studies have suggested that vitamin D levels may be important in how patients respond to pathogens. Studies have linked low vitamin D levels with an increased risk of cancer, particularly colon cancer, in people with IBD. It has also been shown that low vitamin D levels are linked to a higher risk of *Clostridium difficile* infection in the IBD population, which is a significant problem in these patients.

Although some of these data are preliminary, there are laboratory mechanisms supporting the biological possibility of each of these associations. Nevertheless, further studies are needed to demonstrate the consistency of these associations before embarking on therapeutic trials.

G&H Can vitamin D supplementation help prevent relapse or maintain remission in patients with IBD?

AA Several studies have looked at whether vitamin D supplementation keeps Crohn's disease in remission. A Scandinavian study randomized people with Crohn's disease in remission to vitamin D or placebo. At the end of the year, there was a tendency toward lower rates of relapse in people treated with vitamin D compared with placebo. The relapse rate in the vitamin D arm was 13% compared with 29% in patients who received placebo, suggesting that vitamin D may play a role in preventing relapse.

Other studies have looked at vitamin D levels during remission and have suggested that there is a higher risk of relapse in patients with low vitamin D levels. For example, in a study by Gubatan and colleagues, patients in clinical remission with vitamin D levels below 35 ng/mL had a 25% greater risk of relapse over the subsequent 12 months, independent of even endoscopic and histologic activity.

G&H Has there been any research specifically on the effect of vitamin D on disease activity?

AA Very small studies (of 18-20 people) have shown that vitamin D supplementation is associated with improvements in disease activity as well as health-related quality of life. We are just starting to see emerging therapeutic trials of vitamin D supplementation with disease activity as an endpoint. Most studies thus far have looked at bone density as an endpoint because we have been used to thinking of vitamin D as affecting bone density and bone health. However, these emerging data suggest that there should be a focus on the more systemic effects of vitamin D.

G&H Should all IBD patients, including children, receive vitamin D supplementation?

AA All IBD patients, including children, should be assessed for vitamin D deficiency through measurement of 25-hydroxy vitamin D in their blood. In my practice, I do this once a year in all patients. Any patients who have insufficient or deficient levels should receive vitamin D supplementation. Adverse events linked to normal vitamin D supplementation and restoration of normal levels are rare. Of course, clinicians should be aware that taking extremely high levels of vitamin D (several times above normal) may cause adverse effects.

G&H What dose is appropriate in IBD patients?

AA The dose depends on whether a patient is insufficient or deficient in vitamin D. For patients with mild insufficiency, I recommend approximately 1000 to 2000 units of vitamin D per day. In patients who are more deficient, I tend to recommend higher doses, between 2000 and 4000 units daily, until patients develop sufficient levels, at which time I recommend 1000 units per day for maintenance. For many patients with levels of vitamin D less than 20 ng/mL, and certainly less than 15 ng/mL, I use high-dose weekly vitamin D supplementation. For example, ergocalciferol (50,000 units weekly) can be used for 10 weeks to 3 months to get vitamin D levels back to normal.

G&H Should patients taking anti–tumor necrosis factor agents receive vitamin D supplementation to improve response?

AA My colleagues and I, as well as other researchers, have shown that people who are starting anti–tumor necrosis factor (TNF) therapy who are vitamin D–deficient may have lower rates of response or earlier therapy cessation. Whether vitamin D deficiency is a marker of severity influencing response to anti-TNF therapy or whether this is a direct effect of vitamin D augmenting response to these agents is unclear. Thus, I would not recommend vitamin D supplementation just because patients are starting anti-TNF therapy. However, given the possible links between vitamin D and IBD, it may be helpful to supplement vitamin D, although this has not been proven experimentally. At the same time, it is important not to rely on supplementation as the only intervention.

G&H Is vitamin D supplementation as effective as increasing dietary vitamin D?

AA Yes. Both sources of vitamin D, either through supplementation or through diet, are effective. However, increasing dietary intake of vitamin D can sometimes be difficult, particularly in people with IBD who have food sensitivities and gastrointestinal intolerance to dairy products, which are high in vitamin D. Therefore, in many patients, supplementation ends up being the default oral route of vitamin D replacement.

G&H What other vitamin or mineral supplementation is often needed in IBD patients?

AA IBD patients are at an increased risk for a number of vitamin and mineral deficiencies. Vitamin D, iron, and vitamin B12 are frequently low in patients with IBD and, in my opinion, are the most clinically relevant deficiencies in these patients; thus, these 3 nutrients should be systematically measured periodically in patients with IBD. Iron, in particular, is important because people with low iron levels have a lower quality of life, as the deficiency impacts their energy levels.

There are also other micronutrients that may be deficient in patients with IBD. For example, zinc seems to be deficient in IBD patients, although we do not fully understand the implications of this deficiency yet. Clinicians should keep an open mind for deficiencies of other vitamins as well.

G&H What are the next steps in research?

AA The most important next step is to further evaluate the bidirectional relationship of vitamin D deficiency and IBD to definitively determine which one comes first. Because prolonged bowel damage can cause IBD, I think we should not dismiss IBD as merely being a consequence of vitamin D deficiency, particularly with growing evidence and laboratory data suggesting that vitamin D is a potential mediator of several immune responses. I think it is important to understand the role of vitamin D in the treatment of IBD itself, and not just for the treatment of vitamin D deficiency. In particular, this requires rigorous interventional trials that aim to replete vitamin D levels to normal, with disease activity as an endpoint.

We also need to better understand the optimal dose of vitamin D supplementation, and whether there are factors such as genetics that influence response to such supplementation. It is also important to define what the optimal vitamin D level should be in patients with IBD, and whether there should be a different adequate level when looking at inflammation as an endpoint.

G&H Are there any ongoing or upcoming studies in this area that you are anticipating?

AA There are many studies that are just starting to look at vitamin D as a therapeutic intervention in various clinical settings in Crohn's disease and ulcerative colitis. Specifically, studies are examining the role of vitamin D in the induction and maintenance of remission; in conjunction with other therapies, such as anti-TNF agents; and in the prevention of postoperative recurrence. Clinicians are eagerly awaiting data from these studies to help guide clinical practice.

Dr Ananthakrishnan has no relevant conflicts of interest to disclose.

Suggested Reading

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