

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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## Investigating the Role of Vitamin D in IBD Pathophysiology and Treatment

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**G&H** How has the historic research of vitamin D metabolism led to its investigation in connection with inflammatory bowel disease (IBD)?

**YCL** A higher prevalence of vitamin D deficiency has been noted among known IBD patient populations, and other epidemiologic findings have pointed to a connection as well. General epidemiologic study has shown that IBD incidence and prevalence is much higher in North America and northern Europe than in southeast Asia and South America. This discrepancy has been explained, as have similar epidemiologic differences in other diseases, via the “sunlight hypothesis,” which theorizes that North Americans and northern Europeans tend to get less sunlight or ultraviolet (UV) light exposure, which leads to lower rates of vitamin D synthesis and lower systemic vitamin D levels.

In addition, there is a documented role for vitamin D in regulation of immune response. Studies in knockout animal models have shown that vitamin D deficiency leads to activation of T-cell-mediated immune response, thereby linking it to autoimmune disorders, including IBD.

**G&H** How has your own recent research added to this growing body of evidence?

**YCL** Our recently published study demonstrated that vitamin D may play some role in maintaining the integrity of the intestinal mucosal barrier, which is protective against the onset of IBD. Patients with a defect in the mucosa may experience a higher risk of microbial infec-

tion, for example, which may trigger the onset of IBD in patients who are predisposed. Our study showed that vitamin D is able to strengthen the mucosal barrier by upregulating some of the key tight junction and adherens junction proteins. In a vitamin D-deficient state, mucosal barriers are more susceptible to injury that leads to infection and IBD. Thus, vitamin D deficiency could be deemed a contributing factor in IBD, along with genetic predisposition and an infectious event. It could also be termed an environmental factor because vitamin D deficiency tends to be more environmentally mediated than genetically predetermined.

**G&H** Could you describe the factors that may lead to vitamin D deficiency?

**YCL** Several factors can contribute to vitamin D deficiency. Lack of dietary vitamin D can contribute, but dietary vitamin D supplies only 5–10% of the total vitamin D found in humans. Patients who have undergone small bowel resection can also have difficulty absorbing vitamin D, even if they are supplied a vitamin D-enriched diet.

However, most vitamin D comes from sunlight exposure. UV light is necessary for vitamin D synthesis, and lack of UV light is the primary cause of vitamin D deficiency or insufficiency, making geographic location and sunlight exposure more important factors. Older individuals, who tend to stay indoors and have a lower capacity to synthesize vitamin D, often suffer from vitamin D deficiency as well.

**G&H** What level of systemic vitamin D constitutes a deficiency, and what are the physiologic signs?

**YCL** The upper limit of what constitutes deficiency is a complicated issue, engendering much debate. Physicians working in osteopathy point to specific levels of deficiency as causative of many bone problems, including osteomalacia. They suggest that vitamin D levels that trigger raised parathyroid hormone (PTH) constitute deficient status. This phenomenon tends to occur in

patients with 25-hydroxyvitamin D measured at less than 20 ng/mL, an extremely low level.

However, other clinicians not focused on bone disease have noted that although levels above 20 ng/mL may not raise systemic PTH, they may still cause health problems. Because vitamin D has such a broad systemic function, levels higher than 20 ng/mL have been associated with a range of health problems, including hypertension, IBD, and colon cancer.

**G&H** Is there a range of vitamin D deficiency that could be used as part of the screening process for IBD?

**YCL** Physicians might measure vitamin D levels in an IBD diagnosis, but it is not clear how useful a practice this is or if it is a good method for IBD screening.

**G&H** Do you see a potential role for vitamin D therapy in IBD, either as a prophylactic measure in at-risk patients or to help control symptoms in patients with active disease?

**YCL** Prophylactic use of vitamin D therapy in people at high risk for development of IBD is a practice with some potential. Therapy utilizing vitamin D plus calcium has been utilized to prevent colon cancer. Although no clinical trials have yet been conducted in IBD, vitamin D deficiency seems to be a risk factor for some subpopulations of IBD patients. Therefore, raising their vitamin D level could, theoretically, have a protective effect.

Current evidence also points to a role for vitamin D therapy in the treatment of active IBD. Studies in interleukin-10 knockout animals with IBD have shown that administration of vitamin D can ameliorate IBD symptoms. In a human IBD population, although there are no trials as of yet, this therapy could also be an option. The mechanism behind this effect is the known suppression of immune response elicited by vitamin D. Our study demonstrating that vitamin D may strengthen the mucosal barrier shows an additional mechanism that is potentially both protective and therapeutic in active disease.

**G&H** Is vitamin D therapy ready for trial in human subjects with IBD?

**YCL** I am most likely biased in my opinion, but vitamin D has been utilized successfully in clinical trials for other clinical conditions, and IBD is a disease that has been associated with vitamin D deficiency. I think a clinical trial should be conducted in humans as soon as possible.

Studies must also be performed to expand our knowledge of the genetic aspect of vitamin D deficiency. We should pinpoint the genetic defects in the vitamin D endocrine system that control vitamin D absorption and metabolism; this includes enzymes involved in the synthesis and metabolism of the active hormone and the vitamin D receptor. We should find out whether there are DNA polymorphisms or mutations that provide a genetic basis for these conditions. As of yet, there has been little research completed in terms of mapping these processes in IBD patients.

**G&H** Are there any safety concerns that need to be noted or monitored in clinical trials and general administration of vitamin D therapy?

**YCL** Dosing is an important concern, as an overdose of vitamin D carries a risk of toxicity, depending on the form of vitamin D administered. Inactive vitamin D is basically a precursor of the active hormone 1,25-dihydroxyvitamin D and is relatively safe, whereas the active hormone, if overdosed, can raise plasma calcium and cause dangerous levels of hyperglycemia.

However, researchers have synthesized hundreds, if not thousands, of different vitamin D analogs. Most of these are active vitamin D hormones with a much less potent calcemic effect. These are the compounds that are used in clinical trials and for treating patients. Paricalcitol (Zemplar, Abbott Laboratories) is one such compound that is currently on the market. Further, clinical experience has thoroughly established safe levels of these drugs for administration.

## Suggested Reading

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