EDITORIAL

INTESTINAL RESEARCH

pISSN 1598-9100 • eISSN 2288-1956
https://doi.org/10.5217/ir.2019.00038
Intest Res 2019;17(2):157-159

Can vitamin D supplementation help control inflammation in inflammatory bowel disease beyond its classical role in bone health?

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Article: The effect of vitamin D administration on inflammatory markers in patients with inflammatory bowel disease **(Intest Res 2019;17:210-217)**

Inflammatory bowel disease (IBD) is a chronic immune-mediated disorder with a complicated pathogenesis, and with increasing prevalence in both Western and Eastern countries, it has emerged as a public health challenge worldwide.[1] Patients with IBD are known to be at risk for several nutritional deficiencies.[2] Regarding vitamin D and calcium homeostasis patients with IBD have an increased risk of osteopenia and osteoporosis, defined by the umbrella term metabolic bone disease.[3] Several factors, such as malabsorption of calcium and/or vitamin D due to disease flare or surgery, diminished food intake, and medication, can interfere with bone metabolism, while other non-disease-related factors, such as low sunlight exposure, insufficient physical activity, and smoking, may also contribute to vitamin D deficiency in IBD.[4] Vitamin D deficiency appears to be prevalent in IBD patients, with a reported rate ranging from 16% to 95%, and it is more frequent in patients with CD than in those with UC.[3,4] Vitamin D deficiency is traditionally known to cause impaired calcium absorption, negative calcium balance, excessive bone resorption, and consequently metabolic bone disease. Moreover, vitamin D has its own functions in the immunomodulation of both innate and adaptive immunity and influences the gut microbiome beyond the classical role in bone health.[3]

In the current issue of *Intestinal Research*, Jun et al.[5] investigated the association of vitamin D status with CRP level and the partial Mayo score in patients with IBD. In addition, whether vitamin D supplementation could influence the biochemical marker and disease activity was explored. The authors enrolled 88 patients with CD and 178 patients with UC, and serum 25-hydroxyvitamin D_3 [25(OH)D] levels were measured to evaluate vitamin D status. In patients with CD, a negative correlation was found between 25(OH)D and CRP (Spearman's rho = –0.259; 95% CI, –0.427 to –0.078), while no significant correlation of 25(OH)D with CRP or partial Mayo score was reported in patients with UC. Following vitamin D supplementation for 6 months, the 25(OH)D levels significantly increased in both CD and UC patients (11.08 ± 3.63 to 22.69 ± 6.11 ng/mL in CD and 11.45 ± 4.10 to 24.20 ± 6.61 ng/mL in UC). However, this study failed to show a significant effect of vitamin D supplementation on CRP reduction and partial Mayo score between the vitamin D normalized and non-normalized groups in CD and UC. Serum 25(OH)D is the major circulating form of vitamin D, and it is usually used to define vitamin D status in research and clinical practice.[4] Although the threshold for

Received March 28, 2019. **Accepted** March 31, 2019.
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the deficiency level has not been well established in the literature, serum 25(OH)D levels between 20 and 30 ng/mL are considered insufficient and levels ≤20 ng/mL are considered deficient.[3] In the study by Jun et al.,[5] an increase in vitamin D levels after supplementation was shown, but it still did not achieve sufficient levels.

Vitamin D deficiency seems to be inversely linked to disease activity, clinical relapse, frequent hospitalization, and poor quality of life in patients with IBD, although previous studies have reported conflicting data.[3,6] The study by Jun et al.,[5] revealed an inverse correlation between serum 25(OH)D levels and CRP in CD, and a recent study from Korea also revealed a significant inverse correlation of vitamin D levels with disease activity in CD patients.[7] Nonetheless, most of the previous studies were retrospective or cross-sectional in design, thus, they did not answer the chicken or the egg casualty dilemma. Recently, prospective studies have shown an association of low vitamin D levels with clinical relapse, steroid and biologics use, hospitalization, and surgery.[4] In terms of response to biologics, several studies have explored the relationship between 25(OH)D levels and response to anti-TNF inhibitors,[4,6] in which vitamin D levels appear to influence response and durability of anti-TNF therapy. Taken together, these results support the relevance of maintaining adequate levels of vitamin D in patients with IBD in order to improve disease course and response to conventional therapeutics.[3,4,6]

The Western guidelines such as the European Crohn's and Colitis Organisation consensus and the American College of Gastroenterology clinical guideline recommended the assessment of vitamin D levels and supplementation with calcium and vitamin D for the prevention of metabolic bone disease.[8,9] The European Society for Parenteral and Enteral Nutrition guideline also recommended the supplementation of calcium and vitamin D with the rationale that vitamin D deficiency is associated with an increased risk of surgery, hospitalization and *Clostridium difficile* infection in patients with CD and UC in addition to the prevention of osteoporosis.[10] There have been a few randomized controlled trials that support the relevance of the guidelines beyond the classical role of vitamin D in calcium metabolism and bone health, in which vitamin D supplementation reduced CRP level, disease activity, and clinical relapse in IBD.[4] However, the available studies have confounders or limitations; thus, this uncertain area remains to be investigated. The study by Jun et al.,[5] in which the authors unfortunately failed to show the effect of vitamin D supplementation, also has similar limitations such as small sample size, inadequate dose, and possibility of poor compliance. There is no consensus about adequate dose and duration of vitamin D supplementation and follow-up timing of vitamin D measurement to date. Supplementing all patients with the same dose of vitamin D might be inadequate to maintain therapeutic threshold.[4] To clarify these unsolved questions, a well-designed randomized controlled study focusing on the effect of vitamin D supplementation on outcome in IBD is necessary.

FINANCIAL SUPPORT

The authors received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

Writing and approval of final manuscript: Hwang SW.

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https://doi.org/10.5217/ir.2019.00038 • Intest Res 2019;17(2):157-159

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