

Commentary to: “The use of high-dose Omega-3 PUFAs and Vitamin-D co-supplementation as a therapeutic approach for IBD-related symptoms: case report and literature review”

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Inflammatory bowel diseases (IBD) are chronic and invalidating diseases frequently needing continuative immunosuppressive therapy. Available therapies are not free from possible side effects, thus nutritional management is often advocated by patients and doctors as an alternative or an integrative approach to standard medical therapy. Increasing interest has been raised on the role of vitamin D and omega-3 in IBD and other autoimmune diseases. Particularly, vitamin D is low in the IBD population and its immunomodulant effect on both adaptive and innate immunity has been related to IBD pathogenesis. In fact, vitamin D could inhibit the production of the proinflammatory cytokines IL-6 and TNF- α , blocking the p38 MAP kinase in monocytes¹. At the same time, vitamin D could directly have anti-inflammatory properties on T-cell pathways² and promote the gut barrier integrity by regulating the expression of tight junctions and particularly Claudin-2^{3,4}. Furthermore, the dietary intake of vitamin D could positively influence the gut microbiota composition, by increasing the abundance of genera with a potential beneficial effect, such as *Roseburia* and *Alistipes*, particularly in Crohn's disease (CD)^{5,6}. The data from epidemiological and observational studies also suggested a role of vitamin D in IBD. In fact, a meta-analysis estimated that the prevalence of vitamin D deficiency was 38.1% in CD and 31.6% in ulcerative colitis (UC), with a 64% higher odds compared to control and no influence by latitude⁷. Probably, malabsorption is the principal cause of reduced serum levels of vitamin D both during the disease activity and remission phases⁸. In a retrospective longitudinal study on 84 patients, vitamin D deficiency was correlated with poor outcomes in IBD, including

increased disease relapses, hospitalizations, need for steroids and therapy escalation⁸. Similarly, in a Chinese cohort, the vitamin D levels were reduced during severe and moderate flare-ups compared to remission in both UC and CD patients⁹.

Similarly, some epidemiological studies suggested an association between omega-3 and IBD. However, the results from different studies are inconsistent. In fact, some studies suggested a positive correlation between fish and n3-polyunsaturated fatty acids (PUFAs) consumption and risk of IBD, whereas others only found a correlation for n3-PUFAs and not fish or demonstrated a negative or no correlation at all between fish or n3-PUFAs consumption and IBD¹⁰. A recent meta-analysis of observational studies, including 4 prospective and 6 case-control studies, found a negative correlation between the incidence of CD and the dietary content of fish (pooled effect size: 0.54, 95% CI: 0.31-0.96, $p=0.03$) and between the dietary long-chain n-3 PUFAs intake and the risk of UC (pooled effect size: 0.75, 95% CI: 0.57-0.98, $p=0.03$). Instead, no relationship was found between the total dietary n-3 PUFAs intake and IBD (pooled effect size: 1.17, 95% CI: 0.80-1.72, $p=0.41$)¹⁰.

Notwithstanding a strong rationale for the use of vitamin D supplementation in patients with IBD, a conclusive evidence from good quality clinical trials evaluating the effect of vitamin D integration in these patients is lacking. Available data from small, randomized clinical trials failed to demonstrate a positive effect of vitamin D supplementation on clinical disease activity, despite an increase in the serum levels¹¹⁻¹³. Similarly, a meta-analysis of randomized controlled clinical trials failed to demonstrate the efficacy of omega-3 fatty acids in maintaining remission in CD¹⁴.

The clinical case by Boccuzzi et al¹⁵ described a positive example of integration between the standard medical therapy and nutritional support, particularly focusing on vitamin D and omega-3 supplementations in a patient with Crohn's colitis, initially treated with low dose 5-ASA. This case underlines the importance of personalized dietary advice in IBD patients providing the right amount of nutrients and the maximum potential anti-inflammatory effect from the diet. In fact, trying to control symptoms, patients often follow extremely restricted diets autonomously, usually low in vegetables, that could increase bowel movement during active inflammatory phases. Nutritional support should be a constitutive part of a multidisciplinary and individualized approach for these patients, aimed to avoid self-referential dietary restriction and it should be adapted in every patient during the time, based on the phase of the disease and patients' nutritional status. Furthermore, in this clinical case, an attentive nutritional integration with a high dose of vitamin D and ultra-refined EPA and DHA supplement associated to a fish-based Zone diet was reported to improve the clinical symptoms, when associated to standard medical therapy. However, no information was available on the objective markers of inflammation, such as C-reactive protein or endoscopic activity at the end of treatment and the positive effect on symptoms could have been influenced by possible placebo effect.

The role of supplementation of vitamin D and omega-3 to fight the bowel and systemic inflammation is intriguing and supported by a rationale based on preclinical and observational data. Regarding vitamin D, its routine use is already recommended during steroid therapy in patients with IBD to prevent bone loss¹⁶, but our knowledge is still limited regarding possible positive effects on immunomodulation in the clinical setting. Randomized, controlled, and adequately sampled clinical trials are lacking, and they should be recommended to correctly explore the potential therapeutic effect of vitamin D and omega-3 supplementations and to understand how to use it. At the moment, many questions remain open and could limit the routine use of this supplementation in clinical practice. Which is the effective dose? Is it enough to correct the initial deficiency of vitamin D or is higher supplementation required? How long should the treatment be continued? Considering the underlying malabsorption of vitamin D in IBD, could the oral

supplementation be considered as the most suitable route of administration? Could an adequate amount of fish with diet be enough or are specific food supplements required to provide the correct dose of omega-3?

Future research should address these questions to give us the best information to provide an evidence-based approach in the nutritional management of IBD patients and improve patients outcomes.

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