

## Use of Vitamin D3 in Inflammatory Bowel Disease (IBD) Patients: The On-going Saga

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### Editorial

While new options of treatment and management of inflammatory bowel disease (IBD) are being continuously explored [1-3], the introductions of biological products such as infliximab and adalimumab, both of which are tumour necrosis factor (TNF)-alpha inhibitors, have indeed provided therapeutic options for many IBD patients. The likely introductions of other biosimilar versions of both infliximab and adalimumab are expected to bring down the cost of therapy and be more affordable for larger pool of IBD patients [4].

There is a large amount of literature data suggesting that vitamin D3 may have a role to play in scores of diseases including IBD and cancer which is succinctly captured in a recent review [5]. While the consolidated evidence suggested that vitamin D3 may play a role in the pathogenic process of gastrointestinal inflammatory diseases, there has been no clear delineation and/or understanding of the mechanism(s) involved in such reported experimental or clinical investigations [5]. Likewise, another report concluded that supplementation of vitamin D3 reduced the TNF-alpha serum level and thus may have favourably influenced the IBD disease index in patients; without providing more details of the likely mechanism involved [6]. In an interesting earlier work, despite documented beneficial effects of vitamin D3 in IBD patients, it was unequivocally concluded that stronger evidence was necessary to support the role of vitamin D3 in the amelioration of IBD in patients [6].

The clinical study carried out by Ham et al. [7] provided an opportunity to understand the relationship of vitamin D3 levels with disease activity and treatment options in Crohn's disease (CD) patients [7]. The experimental data suggested that following anti-tumour necrosis factor alpha (TNF- $\alpha$ ) therapy (i.e., infliximab), the serum concentrations of vitamin D3 improved as compared to the nadir value prior to the therapy. Because of lack of exogenous supplementation of vitamin D3 in this report, it was judged that improvement in disease condition in itself led to the increased production of vitamin D3 [7]. However, authors proposed that compensatory mechanisms may have occurred to counter the low vitamin D3 levels such as increased CYP27B1 expression to augment vitamin D3 production in the body [7]. In summary, based on the data it may be surmised that infliximab therapy enabled higher circulatory levels of vitamin D3 [7].

In this context, Tajika et al. [8] have performed logistic regression analysis of number of variables deemed important in Japanese patients with CD and concluded that the disease duration was associated with low vitamin D3 levels and this was reflected in the poor CD Activity Index (CDAI) scores observed in the reported study findings [8].

The recent article citing the positive role of vitamin D3 for influencing the remission status of IBD patients is yet another example of therapeutic importance of focussed retrospective clinical data mining from a large database [9]. Despite evaluation being conducted in a single centre with other heterogeneities involved in the procedural aspects of the gathered clinical data set, the authors confirmed that low vitamin D3 exposure may lead to higher odds of not having remission in IBD patients [9]. The IBD patients that showed higher threshold of vitamin D3 levels showed greater odds of remission (OR=2.64, 95% CI=1.31-5.32, P=0.0067) after appropriate stratification/grouping for age, sex, diagnosis, anti-TNF- $\alpha$  drug, and period of exposure to anti-TNF- $\alpha$  drug [9].

Given the above trends, there are number of questions for introspection on the role of vitamin D3 as it relates to IBD which are enumerated below: Firstly, despite such research efforts on the topic, it is somewhat discerning that we still have no unequivocal evidence that would support that vitamin D3 has a direct and independent role in ameliorating IBD without the need of other interventions? Secondly, as documented by scores of literature data, the relationship between vitamin D3 and IBD may be at best categorized to be a cause and effect type; hence, hypothetically speaking would there be a significant clinical benefit of exogenous vitamin D3 treatment to obtain higher odds of treatment improvement including possible remission in IBD patients with or without other pharmacologic interventions? Thirdly, another important and notable disconnect with the observed findings of Winter et al. [9] was the utter lack of clinical effect of vitamin D3 supplementation in IBD patients who already had the first exposure to anti-TNF- $\alpha$  drugs prior to the inclusion in the study data analysis? Fourthly, from the preceding point: would this imply that above and beyond a certain circulatory threshold concentrations of vitamin D3, the beneficial effects of vitamin D3 would cease to exist in IBD patients? Fifthly, additionally in the reported findings of Winter et al. [9] it was rather counter intuitive to imagine as to why second or third introduction to anti-TNF- $\alpha$  therapy failed the odds of IBD patients to have remission despite such patients displayed higher plasma levels of vitamin D3?

Despite the above, it is worthwhile to note that Winter et al. [9] have a well-articulated scientific framework to possibly explain the mechanistic contribution of vitamin D3 in the complex interplay of various inflammatory cytokines. Additionally, in an interesting clinical review, Reich et al. [10] have concluded that risk of relapse of IBD or decreased risk of surgeries in IBD patients could be achieved by augmentation of vitamin D3 levels. Based on this report [10] it appears rather important to have a quantitative estimate of the threshold concentrations of vitamin D3 for its beneficial effects and as well to further delineate the associated remission rates in IBD patients when vitamin D3 is co-administered with IBD therapies such as infliximab

and adalimumab. Therefore, vitamin D3 augmentation prior to and during anti-TNF- $\alpha$  therapy as a treatment strategy needs further evaluation in a larger prospective clinical trial in IBD patients with a clear objective to put this on-going debate to rest.

### Conflict of interest

The author has no conflict of interest to report in the contents of the manuscript (ZRC publication no. 551) which was prepared to promote scientific exchange on an important topic of clinical pharmacology.

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