Microbial Riboflavin Biosynthesis Associates with Response to Dietary Fiber Consumption

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Published in:
Gastroenterology

DOI:
10.1053/j.gastro.2022.10.016

Publication date:
2023

CORRESPONDENCE

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Microbial Riboflavin Biosynthesis Associates With Response to Dietary Fiber Consumption: Time to Personalize Adjunct Therapy in Patients With Inflammatory Bowel Disease?

Dear Editors:

I read with great interest the study by Armstrong et al,[1] who reported on the effects of dietary β-fructan fibers (eg, inulin and fructo-oligosaccharides) in patients with inflammatory bowel disease (IBD) depending on the abundance and fiber-fermenting capacity of microbiota. They demonstrated that β-fructan fibers like inulin remain intact in select patients with active IBD lacking microbial fermentative activities, with subsequent induction of proinflammatory responses mainly through activation of the NLRP3 and TLR2 pathways. Furthermore, microbial cultures revealed that fermentation of β-fructans reduced proinflammatory responses only when microbes were derived from patients with quiescent disease. Interestingly, it was shown that fiber-induced immune responses correlated with microbial functions. Riboflavin synthase, the key enzyme involved in microbial riboflavin biosynthesis, was decreased in ex vivo biopsy cultures of pediatric patients who displayed proinflammatory responses to β-fructans. This observation was further validated through demonstrating that riboflavin was significantly lowered in stool samples collected from ulcerative colitis patients who relapsed upon β-fructan consumption in a randomized controlled trial of ulcerative colitis patients who were in initial remission.[2] In addition, riboflavin was found to negatively correlate with fold-changes in fecal calprotectin. Ultimately, the authors speculated that β-fructan fibers should be administered as adjunct therapy only after medical therapy has induced remission to ensure other benefits of fibers and their products.

The observed association between microbial biosynthetic capacity of riboflavin and the response to β-fructan consumption is very intriguing, because it suggests a critical link between fiber-degrading microbes, the production of short-chain fatty acids, intestinal availability of riboflavin, and response to dietary fibers. Riboflavin is a redox-active vitamin that plays a pivotal role in human energy metabolism and has anti-inflammatory, antioxidant, and microbiota-modulatory properties. As the authors already noted, riboflavin is particularly leveraged by the commensal, butyrate-producing, and inulin-fermenting microbe *Faecalibacterium prausnitzii*. Previous in vitro studies have demonstrated that *F prausnitzii* uses a specialized form of anaerobic metabolism by using riboflavin and thiols for extracellular electron transfer through shuttling electrons to oxygen.[3] As such, *F prausnitzii* reduces its oxygenated microenvironment, thereby preventing oxidative stress and promoting its own growth at the oxic–anoxic interphase of the intestinal barrier.

A recent human study also demonstrated an independent association between extracellular antioxidant capacity (reflected by serum free thiols) and fecal abundance of *F prausnitzii*.[4] Interestingly, we previously uncovered the capacity of *F prausnitzii* to degrade β-fructans, particularly inulin, with resulting anti-inflammatory and cell viability–promoting effects of inulin-derived fructose.[5] In this study, it was demonstrated that bacterial breakdown of β-fructans to simple monosaccharides in the colon provided constant fuel for epithelial cell viability while suppressing inflammation and oxidative stress. Matching these data with findings reported by Armstrong et al[1] would suggest a potential role for riboflavin in determining microbial inulin-degrading capacity.

In addition, in a prospective clinical study investigating the effects of riboflavin in patients with Crohn's disease, we previously reported that riboflavin supplementation resulted in a reduction of systemic oxidative stress, mixed anti-inflammatory effects, and a reduction in clinical symptoms.[6] All these effects were most prominent in patients with active Crohn's disease. In line with findings of Armstrong et al,[1] another study demonstrated that riboflavin biosynthesis pathways were decreased in patients with Crohn's disease exacerbations.[7] These findings implied that a difference in microbial riboflavin-producing capacity may determine a disease-specific response to riboflavin and/or fiber supplementation. Moreover, these data raise the possibility that consumption of β-fructan fibers could be improved by concomitant supplementation of riboflavin and, possibly, related compounds. This could especially be targeted to patients with active disease, as exemplified by increased inflammation, oxidative stress, and microbial disturbances, because in the absence of inflammation and/or disease, these effects are usually reported to be only marginal.[4]

Although the precise mechanisms by which microbial functions such as riboflavin biosynthesis contribute to the response to dietary fiber consumption need to be unraveled, the study by Armstrong et al[1] underscores that adjunct therapy with dietary fibers and/or vitamins should be carefully assessed and optimized for patients with IBD, just as we do for existing medical therapy. The combined presence of a reduced microbial fermentative capacity, increased immune cell activity, disrupted barrier integrity, and oxidative stress could culminate into intestinal inflammation and lead to adverse proinflammatory effects of fiber consumption in patients with IBD. Future studies are warranted to determine whether riboflavin (or related compounds) may enhance microbial fermentative capacity and if

this could help to determine which patients would benefit most from fiber consumption or could better avoid it.

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References

1. Armstrong HK, et al. Gastroenterology 2023; 164:228–240.
2. Valcheva R, et al. medRxiv 2022.01.16.22269376.
3. Khan MT, et al. ISME J 2012;6:1578–1595.
4. Bourgonje AR, et al. Free Radic Biol Med 2022; 190:169–178.
5. Fagundes RR, et al. Gut Microbes 2021;13(1):1993582.
6. von Martels JZH, et al. J Crohns Colitis 2020; 14:595–607.
7. Klaassen MAY, et al. J Crohns Colitis 2019; 13:1439–1449.

Conflicts of interest
The author discloses no conflicts.

Most current article

https://doi.org/10.1053/j.gastro.2022.10.016

Reply. We read with great interest the compelling summary and excellent ideas raised by Dr Bourgonje in response to our recent findings published in *Gastroenterology* in 2023.[1] Dr Bourgonje elaborated on our discussions of the potential link between microbial riboflavin biosynthesis and dietary β-fructan fiber sensitivity in inflammatory bowel diseases (IBDs). Our work was stimulated by a chief complaint of IBD patients, that a high-fiber diet is not well tolerated in some patients, particularly during disease flare.[2] Importantly, we showed that although dietary fibers are typically considered beneficial in individuals with normal microbial fermentative potential,[3] specific dietary fibers, if not fermented by gut microbiota, can elicit inflammation and gut damage.[1] Clinically, this is well recognized because no fiber diet therapies (eg, exclusive enteral nutrition) improve disease outcomes, whereas low-FODMAP diets can reduce symptoms in IBD patients.[4,5] However, a thorough mechanistic understanding regarding which fibers, which patients, and why the intolerance occurs is still lacking, and our findings and those of others support how microbiome may be the key.[1]

β-Fructans are more difficult to ferment than the more readily metabolized dietary fibers (pectins, cellulose, and xylans); this perhaps is due to the limited number of specific microbiota (eg, *Lactobacillus* and *Bifidobacterium*) that are capable of metabolizing β-fructans.[6] An abundance of microbes known to ferment fibers (such as *Roseburia hominis* and *Faecalibacteria prausnitzii*) is significantly reduced in patients with active IBD,[3] and our findings demonstrate that microbiota functions were significantly associated with host response to β-fructans.[1] Riboflavin synthase was 1 of the key microbial enzymes found to be associated with an adverse response to β-fructans in IBD patients. It is important to note that the microbial enzyme riboflavin synthase was not lowered in biopsies from IBD patients (representing mostly host genes), but rather *microbial* riboflavin synthase was found to be lower in whole microbiota gut washes (measured by shotgun metagenomics) from pediatric patients whose paired gut biopsies displayed increased proinflammatory responses to β-fructans. As mentioned by Dr Bourgonje, we validated the association of riboflavin with patient response to consumption of β-fructans in stool samples collected at baseline in our randomized control trial cohort; patients who flared after a 6-month consumption of β-fructans (15 g/day) had significantly lower stool riboflavin levels at baseline, compared with those who did not flare.

The work mentioned by Dr Bourgonje is certainly in line with our hypothesis and findings, and we welcome the suggestion made on implications of these studies. Importantly, prior studies of riboflavin supplementation in IBD patients remain preliminary and display only limited significant findings, exclude important statistical analyses, and lack appropriate placebo control subjects.[7] Larger studies over a longer time period are needed to the confirm true clinical relevance of riboflavin utility in IBD, yet our study presently supports the use of riboflavin as a potential biomarker of gut response to β-fructans rather than use of riboflavin as a supplement. Although our findings support a role for microbe-altering therapies that promote regrowth of microbiota that produce the riboflavin synthase enzyme in eliminating the negative impact of dietary β-fructan fibers, we certainly support the idea that co-treatment with riboflavin (for select patients) could also possibly achieve this.[1] We believe the microbes themselves are key, but a personalized approach combining nutritional interventions is certainly attractive.

Ultimately, we demonstrated that a specific set of IBD patients, particularly those experiencing disease flare who have altered microbiota and an inability to ferment specific fibers, could adversely respond to β-fructans. Our findings suggest that those patients should avoid high consumption of β-fructans until their microbiota is capable of using these fibers appropriately. Clinical studies performed to date support our mechanistic data, demonstrating that β-fructan consumption in select IBD patients can worsen outcomes.[8] Furthermore, clinical trials evaluating the impact of prebiotic fibers in IBD are limited and primarily demonstrate that benefits of dietary fibers are associated with short-chain fatty acid production and successful fiber fermentation.[3] The association with microbial riboflavin biosynthesis and the potential for adjunct therapy in select patients to help overcome the IBD-associated dysbiosis warrant further research and are exciting extensions of our work. Uncovering the precise interactions of gut microbiota, their functional capacity, dietary fiber subtypes,