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EDITORIAL

Which Environmental Factors Cause IBD Relapses?

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During the past 20 years, much progress has been made in multiple inflammatory bowel disease (IBD)-related fields such as in genetics, disease mechanisms, microbiota composition, cytokines, and cell populations, all of which are involved in the deregulated gut immune response. In parallel, biologic drugs have improved management of IBD patients. Nevertheless there is also strong evidence that living conditions and environmental factors contribute significantly to IBD occurrence and pathogenesis. The marked increase of IBD incidence in many countries in recent decades is incompatible with a purely genetic disease [1–3]. Also, data from migration studies indicate that second-generation immigrants manifest the risks of their new environment [4]. Established IBD risk factors include smoking, appendicitis, and antibiotics. Recently, several groups also identified diet as a possible risk factor [5]. While there is some knowledge of suspected IBD environmental risk factors involved in disease occurrence, even less is understood about risks of disease relapses. This critical lack of knowledge seriously limits the development of preventive approaches in IBD. Yet, preventive actions are certainly urgent needs for the following reasons:

- Current IBD treatments are based primarily on costly anti-inflammatory, immunosuppressant, and biological drugs, which have severe adverse events that limit their use, especially in the context of lifelong disorders.
- IBD is a major public health problem; therefore, any preventive action that could even modestly reduce the relapse rate and incidence of the disease would have a significant economic impact.
- There is a strong community demand for recommendations for an activist approach toward disease prevention.

The paper by Martin et al. [6] published in this issue of *Digestive Diseases and Sciences* critically appraises the scarce evidence supporting the associations between environmental factors and IBD course. They report consistent associations between disease flares and smoking in Crohn's disease (CD) (inverse in ulcerative colitis [UC]). There is no consistent association between the use of estrogens and IBD relapse. One study from the UK General Practice Research Database reported an inverse association between antibiotic use and the risk of relapse in CD. A prospective study from Canada reported a positive association between psychological stress and clinical relapse, but the association was no longer significant when the diagnoses of relapses were certified by increased fecal calprotectin levels (Bernstein CN, oral communication ECCO 2014). Moreover, one study described an ecological correlation between air pollution and hospitalizations for IBD. Martin et al. point out that the literature dedicated to the association between NSAIDs and the risk of relapse is open to criticism. However, there is one clinical trial of NSAIDs

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which showed that 20 % of patients experienced a disease after NSAID ingestion [7]. It seems that cyclooxygenase (COX)-2-selective NSAIDs are not associated with IBD relapse [8].

Some data also suggest that diet may influence IBD course. Firstly, enteral nutrition may induce clinical remission and mucosal healing, especially in children. Secondly, a UC cohort of 200 patients with a 1-year follow-up, assembled with the specific aim of finding dietary factors associated with relapse, identified sulfur-rich nutrients (including meat) as a risk factor for relapse [9], in line with the paper by Jantchou et al. [10] who reported that high amounts of dietary animal protein increased the risk of CD and UC. It is also consistent with the questionnaire-based survey of German IBD twins describing a relationship between meat consumption and IBD [11], observations reminiscent of the "cold chain" hypothesis that we proposed several years ago [12] in which we theorized that the increase in CD incidence could be explained by the development of refrigeration, which promotes the growth of psychrotrophic bacteria such as nonpathogenic strains of *Yersinia* or *Listeria* in refrigerated food. These bacteria interact with the NOD2 gene product and therefore may participate to CD pathogenesis [13, 14]. Meat and fish harbor high counts of psychrotrophic bacteria, particularly true for cooked products in self-service restaurants. Thirdly, a small open clinical trial has suggested that a traditional Japanese semi-vegetarian diet could be effective in preventing CD relapse [15].

Many IBD patients have inadequate dietary intake due to food intolerance, which is often reported by patients although the food items perceived as "offending" are usually inconsistent between patients. A Canadian study reported that IBD patients avoid alcohol, popcorn, legumes, nuts, seeds, deep-fried food, and processed meat [16]. Patients with active IBD also consumed significantly more portions of sports drinks and sweetened beverages compared with those with inactive disease [16]. A recent study revealed that the preillness diet of UC patients contained soft drinks than that of controls (Racine et al. submitted). Although physicians often advise their patients to eat a low-residue diet during disease flares, IBD subjects often continue to avoid eating fruits and vegetables when in remission. Nonetheless, a diet poor in fruits and vegetables is associated with reduced microbial diversity which has been correlated with steroid resistance and a poor prognosis in children with UC [17]. Since a low-residue diet is therefore counterintuitive, many IBD specialists recommend that their patients eat a "normal" diet, at least when in remission.

How do these data translate into clinical practice?

1. In a study published in 2001, ex-smokers were reported to have a disease course similar to that of nonsmokers and significantly better than that of active smokers [18]. A recent paper confirmed that, in the era of biologics, smoking is still associated with a poor prognosis, such as stricturing disease and perianal complications in CD subjects [19]. Yet, the long-term rate of smoking cessation is only 23 % [20], no better than smoking cessation rates in smokers without CD [21]. CD patients should be informed of the deleterious effect of smoking over their disease course, with full access to smoking cessation programs, including counseling, pharmacotherapy, and possibly alternative medicine such as hypnotherapy [22].
2. There is no reason to discourage the use of estrogens and antibiotics in IBD patients. More caution is needed regarding the use of NSAIDs in patients with IBD.
3. Unfortunately, we are yet unable to make dietary recommendations to IBD patients. Dietary therapy is already a major therapeutic tool as an induction treatment in CD but is unpractical as a maintenance therapy. A diet poor in ω-3 fatty acids has been associated with a diminished risk of having CD and UC, but a randomized trial did not show any benefit for an oral supplementation in ω-3 fatty acids in patients with CD [23]. Hypothetically, diet might contribute to correct the dysbiosis associated with IBD and to improve the disease course. Indeed, dietary intake influences the structure and activity of human gut microbiota, in the short and long terms [24, 25].

To better advise our patients, there is certainly a need for additional studies to further explore the link between environmental factors—including dietary habits—and gut microbiota composition, fecal and serum biomarkers and ultimately disease course.

References

1. Ng SC, et al. Geographical variability and environmental risk factors in inflammatory bowel disease. Epidemiology and natural history task force of the international organization of inflammatory bowel disease (IOIBD. *Gut*. 2013;62:630–649.
2. Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*. 2011;140:1785–1794.
3. Jantchou P, Monnet E, Carbonnel F. Environmental risk factors in Crohn's disease and ulcerative colitis (excluding tobacco and appendicectomy). *Gastroenterol Clin Biol*. 2006;30:859–867.
4. Probert CS, et al. Epidemiological study of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire. *Gut*. 1992;33:687–693.
5. Andersen V, et al. Diet and risk of inflammatory bowel disease. *Dig Liver Dis*. 2012;44:185–194.
6. Martin TD, Chan SM, Hart A. Environmental factors in relapse and recurrence of inflammatory bowel disease. A review of the

literature. *Dig Dis Sci*. (Epub ahead of print). doi:10.1007/s10620-014-3437-3.
7. Takeuchi K, Smale S, Premchand P, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2006;4:196–202.
8. Kvasnovsky CL, Aujla U, Bjarnason I. Nonsteroidal anti-inflammatory drugs and exacerbations of inflammatory bowel disease. *Scand J Gastroenterol*. 2014;14:1–9.
9. Jowett SL, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. *Gut*. 2004;53:1479–1484.
10. Jantchou P, et al. Animal protein intake and risk of inflammatory bowel disease: the E3N prospective study. *Am J Gastroenterol*. 2010;105:2195–2201.
11. Spehlmann ME, Begun AZ, Saroglou E, et al. Risk factors in German twins with inflammatory bowel disease: results of a questionnaire-based survey. *J Crohns Colitis*. 2012;6:29–42.
12. Hugot JP, et al. Crohn's disease: the cold chain hypothesis. *Lancet*. 2003;362:2012–2015.
13. Kobayashi KS, et al. Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. *Science*. 2005;307:731–734.
14. Meinzer U, et al. Yersinia pseudotuberculosis effector YopJ subverts the Nod2/RICK/TAK1 pathway and activates caspase-1 to induce intestinal barrier dysfunction. *Cell Host Microbe*. 2012;11:337–351.
15. Chiba M, et al. Lifestyle-related disease in Crohn's disease: relapse prevention by a semi-vegetarian diet. *World J Gastroenterol*. 2010;16:2484–2495.
16. Vagianos K, Clara I, Carr R, Graff LA, Walker JR, Targownik LE, Lix LM, Rogala L, Miller N, Bernstein CN (2014) What are adults with inflammatory bowel disease (IBD) eating? A closer look at the dietary habits of a population-based Canadian IBD cohort. *JPEN J Parenter Enteral Nutr*. (2014). doi:10.1177/0148607114549254.
17. Michail S, Durbin M, Turner D, et al. Alterations in the gut microbiome of children with severe ulcerative colitis. *Inflamm Bowel Dis*. 2012;18:1799–1808.
18. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology*. 2001;120:1093–1099.
19. Nunes T, Etchevers MJ, Domènech E, et al. Tobacco-Eneida Study Group of GETECCU. Smoking does influence disease behaviour and impacts the need for therapy in Crohn's disease in the biologic era. *Aliment Pharmacol Ther*. 2013;38:752–760.
20. Nunes T, Etchevers MJ, Merino O, et al. High smoking cessation rate in Crohn's disease patients after physician advice–the TABACROHN Study. *J Crohns Colitis*. 2013;7:202–207.
21. Walker N, Howe C, Glover M, et al. Cytisine versus nicotine for smoking cessation. *N Engl J Med*. 2014;371:2353–2362.
22. Tahiri M, Mottillo S, Joseph L, Pilote L, Eisenberg MJ. Alternative smoking cessation aids: a meta-analysis of randomized controlled trials. *Am J Med*. 2012;125:576–584.
23. Feagan BG, Sandborn WJ, Mittmann U, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC randomized controlled trials. *JAMA*. 2008;299:1690–1697.
24. Wu GD, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011;334:105–108.
25. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505:559–563.