

Missing Environmental Factor in Inflammatory Bowel Disease: Diet-associated Gut Microflora

To the Editor:

Disease occurs as a result of the interaction between genetic factors and environmental factors. The majority of common diseases are multifactorial polygenic diseases. Inflammatory bowel disease (IBD), a collective term for Crohn's disease (CD) and ulcerative colitis (UC), is also known as a polygenic disease in which the contribution of each gene to the onset of disease is small. Susceptibility genes identified in IBD involve recognition of microbial agents, bacterial clearance, mucosal barrier function, and immunoregulation.¹ Development of IBD in genetically susceptible subjects is triggered by environmental factors.¹ Since the human genetic constitution has hardly changed over its long history, the abrupt increase in IBD incidence during the transition from a "developing" to "developed" nation² can be explained not by genetic factors but by changes in environmental factors. Some of the environmental factors that have been observed in association with IBD include cigarette smoking, the use of oral contraceptives, stress, and appendectomy.^{1,2} However, these environmental factors are thought to play only a mediating role in IBD. A real key environmental factor has not been identified. Consequently, there is no particular lifestyle recommendation in guidelines except for smoking cessation in CD.

We tend to recognize things outside the body as environmental factors.

Copyright © 2011 Crohn's & Colitis Foundation of America, Inc.

DOI 10.1002/ibd.21745

Published online 3 May 2011 in Wiley Online Library (wileyonlinelibrary.com).

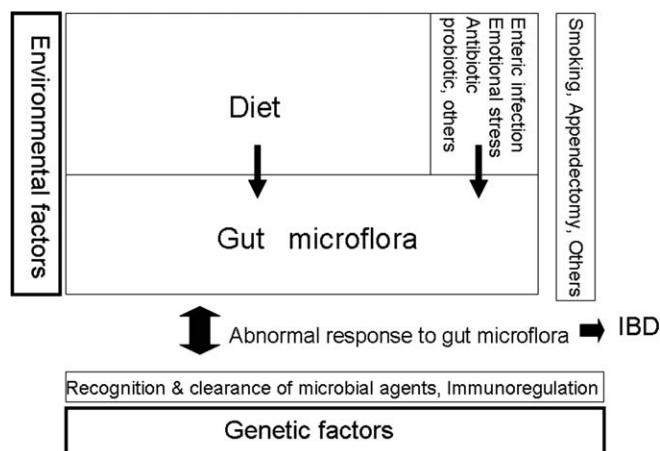


FIGURE 1. Schematic pathogenesis of IBD. IBD occurs in genetically susceptible persons when triggered by environmental factors. The most critical environmental factor is gut microflora, which is formed by diet. Namely, diet-associated gut microflora is the greatest environmental factor in IBD.

However, recent studies have identified intestinal microflora, inside the body, as an environmental factor for obesity.³ The presence of gut indigenous microflora is a prerequisite for gut inflammation.^{1,4} In addition, IBD is thought to result from an inappropriate response of the mucosal immune system to gut microflora.^{1,4} Therefore, gut microflora should be the environmental factor most responsible for IBD. Indeed, dysbiosis, an imbalance of microflora, i.e., a decrease in beneficial (preventive) bacteria and an increase in potentially pathogenic bacteria, is observed in patients with IBD and can be a trigger for onset or relapse of IBD.^{1,4} Gut microflora is modified by diet, antibiotics, enteric infection, and emotional stress, etc. Meals with different dietary patterns form different patterns of gut microflora.¹⁻⁴ IBD is prevalent in wealthy nations² where dietary Westernization inevitably occurs.⁵ Dietary Westernization is characterized by increased consumption of animal protein, animal fat, and sugar, with decreased consumption of grains.⁵ Diets rich in animal protein and animal fat cause a decrease in beneficial bacteria in the intestine.^{4,6}

The latest studies clearly show that manipulation of meals influences

the relapse rate of CD. A half-elemental diet (ED), i.e., replacement of half of the daily energy intake with ED, significantly suppresses the relapse rate at 1 year (a half ED versus a free diet: 26.9% versus 64.0%).⁷ A semivegetarian diet designed to increase the number of beneficial bacteria keeps remission at 100% the first year and at 92% the second year (omnivorous diet: 67% and 25%, respectively).⁶ These preventive effects of dietary manipulation against relapse are far better than those obtained by current drugs, including biological agents.⁸ Most follow-up studies on IBD to date lack analysis of diet or diet-associated gut microflora. Unpredictability of the prognosis in IBD, particularly in CD, will be greatly improved by the analysis of diet or diet-associated microflora.

A concept is needed that the greatest environmental factor in IBD is (diet-associated) gut microflora (Fig. 1).

Mitsuro Chiba, MD, PhD
Hidehiko Tsuda, MD
Toru Abe, MD
Takeshi Sugawara, MD
Yoshihide Morikawa, MD

Division of Gastroenterology
 Nakadori General Hospital
 Akita, Japan

REFERENCES

1. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol.* 2006; 3:390–407.
2. Bernstein CN, Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. *Gut.* 2008;57:1185–1191.
3. Ley RE, Turnbaugh PJ, Klein S, et al. Microbial ecology: human gut microbes associated with obesity. *Nature.* 2006;444: 1022–1023.
4. Tamboli CP, Neut C, Desreumaux P, et al. Dysbiosis in inflammatory bowel disease. *Gut.* 2004;53:1–4.
5. Report of the Working Group on Arteriosclerosis of the National Heart, Lung, and Blood Institute. *Arteriosclerosis.*, vol. 2. 1981.
6. Chiba M, Abe T, Tsuda H, et al. Lifestyle-related disease in Crohn's disease: Relapse prevention by a semi-vegetarian diet. *World J Gastroenterol.* 2010;16:2484–2495.
7. Takagi S, Utsunomiya K, Kuriyama S, et al. Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: a randomized-controlled trial. *Aliment Pharmacol Ther.* 2006;24:1333–1340.
8. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* 2010;362:1383–1395.