Environmental Influences on the Onset and Clinical Course of Crohn's Disease—Part 1: An Overview of External Risk Factors

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Abstract: The pathogenesis of Crohn's disease (CD) involves host, genetic, and environmental factors. These factors result in disturbances in the innate and adaptive immune systems and composition of the intestinal microbiota. Epidemiologic and migration studies support an environmental component in the development of CD. Environmental risk factors include childhood hygiene, air pollution, breastfeeding, smoking, diet, stress, exercise, seasonal variation, and appendectomy. This review, part 1 of a 2-part series, provides an overview of these external contributors to the development or exacerbation of CD. Part 2, which will be published in a subsequent issue, will discuss the influences of infections, vaccinations, and medications (including antibiotics, nonsteroidal anti-inflammatory agents, and oral contraceptives) on CD.

Keywords
Crohn's disease, environmental factors, inflammatory bowel disease, infection, pathogenesis, medications

Inflammatory bowel disease (IBD) is a chronic, relapsing, and remitting disease of the gastrointestinal tract manifesting as Crohn's disease (CD) or ulcerative colitis (UC). The development of IBD involves a complex interplay between genetic predisposition and the environment. Genetic factors have been well documented as contributing to the pathogenesis of CD; however, twin studies have shown an important environmental influence on CD.[1] Several epidemiologic studies have demonstrated a rising incidence of CD and geographic variation over the past several decades, suggesting an environmental impact on the pathogenesis of IBD.[2,3] It has been speculated that environmental factors can influence intestinal permeability, alter the mucosal immune system, and disrupt the intestinal microbiota, thereby creating a predisposition to IBD.[4] This review, part 1 of a 2-part series, will focus on these environmental risk factors, including childhood influences, lifestyle choices, seasonal variation, and appendectomy, on the development or exacerbation of CD. Part 2, which will be published in a subsequent issue, will focus on the microbiota and the influences of infections, immunizations, and medications on CD. The Table summarizes childhood, lifestyle, perinatal, and environmental factors.

Table. The Influence of Lifestyle Factors on CD: Key Points

Breastfeeding • Meta-analyses demonstrate conflicting data on the protective effect of breastfeeding on the onset of CD.[13,17] • The protective effect may be related to the duration of breastfeeding, with a threshold between 3 to 6 months.[7,19]
Smoking • Cigarette smoking is a risk factor for CD[23,24] and has a negative effect on disease course.[25-30] • Smoking cessation leads to improved clinical outcomes.[30,35,36]
Diet • High intake of polyunsaturated fatty acids, saturated fats, omega-6 fatty acids, and meat increases the risk of CD, and high intake of dietary fiber and fruits decreases the risk of CD.[44] • There are insufficient data to recommend omega-3 fatty acids for maintenance of CD remission.[56]
Mental Health • High perceived stress and ineffective coping strategies have been linked to disease exacerbation in IBD.[63,64] • Patients with IBD should be routinely screened for depression and anxiety at the time of diagnosis, during periods of active disease, and after IBD-related surgeries or hospitalizations.[65,73-75] • Sleep disturbance is common among patients with active and inactive IBD and can lead to an increased risk of disease flares.[76]
Exercise • Physical activity is reduced among patients with IBD.[81,82] • Quality of life is improved and stress is reduced in patients with CD who engage in regular low-intensity exercise.[84-86]

CD, Crohn's disease; IBD, inflammatory bowel disease.

Childhood Factors

Hygiene Hypothesis

As developing countries become more industrialized with improved sanitary conditions, patterns of childhood hygiene have changed. It has been hypothesized that these changes in hygiene may result in decreased exposure to microbial agents in the environment and contribute to dysbiosis or an alteration in the balance between commensal and pathogenic intestinal bacteria.[5] Bacterial diversity has been reported to be low in patients with IBD. Specifically, patients with CD have been consistently observed to have a reduction in microbes of the phylum Firmicutes (gram-positive bacteria, including *Clostridium* and *Bacillus* species) and a concomitant increase in Proteobacteria (gram-negative rods, including *Escherichia* species).[6] The disruption in the intestinal microbiota may be involved in the initiation and perpetuation of inflammation in IBD.

Several epidemiologic studies have looked at various proxy measures for microbial exposure in patients with CD. Domestic factors, including urban upbringing,[7,8] hot water supply,[9,10] and separate bathrooms,[10] have been associated with CD. Additional markers such as large family size[8] and pet exposure[11] have been noted to be protective, although findings have been conflicting.[12] Other surrogate markers that have been studied include gestational age at birth, birth weight, birth order, and sibship. Thus far, no single hygienic factor has demonstrated a consistent association with IBD.[9,10,13]

Air Pollution

In industrialized regions, in addition to hygiene, there is increasing evidence for the role of environmental air pollution as a risk factor for CD. Animal models have suggested that air pollutants may create a proinflammatory response, exert a direct effect on epithelial cells, and change the composition of the gut microbiota in the host.[14] In epidemiologic studies, traffic-based pollutants (including nitrogen dioxide) have been associated with the development of early-onset CD.[15] In another study, a correlation was found between ambient air pollution and the rate of IBD hospitalizations.[16]

Breastfeeding

Breast milk contains many components that impact immune tolerance and bacterial colonization of the gut. These effects on the immune system and the intestinal microbiota at an early age have been implicated in the development of IBD. The protective effects of breastfeeding are unclear. A meta-analysis on the effects of breastfeeding on pediatric and adult-onset IBD showed a statistically significant protective effect of breastfeeding on CD with an odds ratio (OR) of 0.67 (95% CI, 0.52-0.86).[17] A subsequent meta-analysis focused exclusively on the effects of breastfeeding on early-onset IBD and showed a significant protective effect of breastfeeding for both IBD subtypes (OR, 0.69; 95% CI, 0.51-0.94; *P*=.02), although there was a nonsignificant difference with CD individually.[18]

The protective effects of breastfeeding may be related to the duration of breastfeeding. A population-based, case-control study conducted in New Zealand showed a protective effect only after a minimum of 3 months of breastfeeding.[7] Another study in Denmark incorporated duration as a variable and observed a trend toward a decreased risk of CD in persons who have been breastfed for more than 6 months.[19] However, in a recent prospective study, this durational effect was not observed.[20]

In nursing mothers with IBD, there are limited data evaluating the effect of breastfeeding on disease course. Discontinuation of medications and resumption of smoking are important factors that can lead to worsening of disease activity in the postpartum period.[21] Given the conflicting data, no firm conclusions can be made regarding breastfeeding's effect on the development of CD or in causing disease flares in the postpartum period.[22]

Lifestyle Factors

Smoking

Smoking is a recognized risk factor for CD,[23,24] and patients with CD have higher rates of tobacco use than the general population.[25] Compared with nonsmokers, patients with CD who smoke suffer more clinical relapses,[25,26] experience more intestinal complications,[27,28] have higher rates of surgery,[29,30] and need more immunosuppressive therapy.[25,31] In addition, increased pack-years is associated with increased risk of CD,[24] and heavy smokers have been observed to have worse clinical outcomes compared with light smokers.[30,32,33] Interestingly, women appear to be more susceptible than men to the harmful effects of smoking in CD.[34]

Smoking cessation reduces the risk of relapse[35] and postoperative recurrence of disease.[30] Importantly, reducing the number of cigarettes may not be sufficient to improve clinical outcomes, as even light smoking has been shown to have deleterious effects.[32] Compared with active smokers, patients who successfully quit smoking for more than 1 year appear to significantly reduce their risk of experiencing a flare, as well as the need for the use of corticosteroids or immunomodulators.[36] Based on these findings, smoking cessation should be strongly encouraged.

Diet and the Onset of Crohn's Disease

Food can be considered a gut antigen that can influence mucosal inflammation and alteration of the intestinal microbiota. A Western diet high in fat and carbohydrates and low in fiber has been speculated to play a role in the rising incidence of CD.[4,37] Additionally, vitamin D deficiency may have a role in the development of CD or disease activity, and supplementation may have a benefit.

Carbohydrates Early case-control studies on patients in whom CD was recently diagnosed demonstrated an increased intake of sugar compared with controls,[38-40] although this may be secondary to increased sugar consumption during flares.[41] Due to methodologic deficiencies in the literature, there is insufficient evidence to link high sugar intake with the development of CD.[41] Further prospective data are needed, given these conflicting findings.[19,42,43]

Protein The data on the association between protein intake and the development of CD are unclear. A recent meta-analysis reported that the majority of studies have shown a positive association with CD, but statistical significance has not been achieved in many of these studies.[44] One recent population study in middle-aged French women showed that high total protein intake, specifically animal protein (both fish and meat), was associated with a significantly increased risk of IBD (hazard ratio [HR] for the third vs first tertile, 3.03; 95% CI, 1.45-6.34).[45]

Fruits and Vegetables Fruits and vegetables are a source of dietary fiber and may have a protective effect through their antioxidant properties and clearing of reactive oxygen species.[42] A diet low in raw fruits and vegetables is more frequently seen in patients with CD.[39,46] In a pediatric study of patients in whom CD was diagnosed prior to age 20 years, children who consumed a higher amount of fruits and vegetables were at a lower risk than others for the development of CD, with a significant dose-response effect with increasing consumption.[42] These findings were further supported in a meta-analysis that demonstrated a decreased risk of CD with high fiber and fruit intake.[44] The protective effect of fiber, though, appears to be related to the source of fiber. Dietary fiber (fruits and vegetables) was associated with a reduced risk for CD in the Nurses' Health Study, but insoluble fiber (whole grain and bran) did not have the same association.[47]

Fat Intake and Obesity Epidemiologic studies in Japan have shown that increased dietary intake of animal protein and long-chain omega-6 polyunsaturated fatty acids may contribute to the development of CD.[48] Long-chain omega-6 fatty acids are found in beef, pork, corn, food oils, and polyunsaturated margarine. Linoleic acid, an omega-6 fatty acid, is metabolized to arachidonic acid. Metabolites of arachidonic acid are involved in the production of inflammatory mediators such as leukotrienes and prostaglandins.[49] Higher consumption of food made up of omega-3 fatty acids (ie, fish oils) results in a higher ratio of omega-3 to omega-6 fatty acids and has shown to be protective in children with CD.[42] A recent meta-analysis reported an increased risk of CD with high intake of polyunsaturated fatty acids, saturated fats, omega-6 fatty acids, and meat.[44] Further prospective studies are needed to determine whether a higher ratio of omega-3 to omega-6 fatty acids is protective for CD.

Obesity, which has been increasing, is suspected of being associated with a Western diet and can lead to a proinflammatory state. A subcohort of the EPIC study (European Prospective Investigation into Cancer and Nutrition) identified 75 patients with incident CD out of 300,724 subjects and measured body mass index (BMI)

in all subjects at enrollment. After adjusting for smoking, energy intake, and physical activity, BMI was not associated with incident CD.[50]

Vitamin D Vitamin D deficiency has been associated with CD, although it is unclear whether this is a consequence of malabsorption or an underlying cause of CD. Using a vitamin D predictive formula in a subcohort of the Nurses' Health Study, women with the highest quartile of vitamin D levels had half the incidence of CD compared with women in the lowest quartile (HR, 0.54; 95% CI, 0.30-0.99).[51] A European study on common polymorphisms of the vitamin D receptor gene did not show an effect on the development of CD.

Diet and the Course of Crohn's Disease

The data on the role of diet on disease course in CD have been more limited. A survey of persons in the Crohn's and Colitis Foundation of America Patients as Partners Internet-based cohort study provided information regarding foods thought to ameliorate or exacerbate disease activity. Yogurt and rice were more frequently reported to improve symptoms, whereas fruits, vegetables, high-fiber foods, red meat, fried foods, spicy foods, popcorn, nuts, milk, soda, and alcohol were more frequently reported to worsen symptoms in patients with CD.[52] Ultimately, pooling food intolerance data can help generate hypotheses to test in prospective trials to determine whether particular agents have a true impact on disease course.[52]

Vitamin D deficiency also has been suspected to affect disease activity. A randomized, double-blind, controlled study by Jørgensen and colleagues found that oral vitamin D3 taken at 1200 IU daily for 12 months resulted in increased serum vitamin D levels in patients with CD and that the relapse rate was lower among those patients receiving vitamin D3 supplementation than those who were not (13% vs 29%; P=.06).[53] Further research is needed on the therapeutic potential of vitamin D3.

From a management perspective, there are also various dietary interventions that have been studied in CD. A prospective study assessing the value of a low-sugar, high-fiber diet showed no significant benefit in altering the clinical course in patients with quiescent or mildly active CD.[54] Clinical practice is to recommend a low-residue diet in those patients with fibrostenotic CD and concern for impending obstruction, although an Italian study failed to show benefit from such a practice.[55] Another proposed intervention strategy is administration of omega-3 fatty acid, given its anti-inflammatory properties. A recent systematic review, however, concluded that there are insufficient data to recommend the use of omega-3 fatty acid supplementation for maintenance of remission in CD.[56] Enteral nutrition also has been evaluated for the management of IBD. In adults, enteral nutrition is less effective than corticosteroid therapy in achieving clinical remission in active CD,[57] although, in children, both treatments appear to have similar efficacy.[58] Enteral nutrition in conjunction with current medical therapy for maintaining remission will be an area of interest in future clinical studies.[59]

Stress, Depression, Anxiety, and Sleep

Patients often perceive that stress plays a significant role in the onset and course of their IBD.[60,61] In animal models of acute stress, investigators observed changes in mucosal inflammation, intestinal permeability, colonic motility, and the bacterial-host relationship.[62] In humans, studies have been less convincing and have been limited by methodologic deficiencies, although perception of stress and ineffective coping strategies (eg, social diversion or distraction activities) may play a more important role in predicting time to relapse in patients with IBD.[63,64]

Depression and anxiety also have been found to be associated with CD.[65-67] The lifetime prevalence of major depressive disorder (MDD) in patients with IBD is as high as 27% compared with 12% in matched controls,[66] and in clinical trials, MDD is a predictor of failure to achieve remission.[68] Data from the Nurses' Health Study suggest that depressive symptoms conferred a 2-fold increased risk for CD and may suggest a biopsychosocial model for the pathogenesis of IBD.[69] Increasing evidence also suggests that depression and anxiety may have effects on disease activity and relapse in CD,[65,70,71] although the data are conflicting.[72]

Clinicians should be aware of the increased prevalence of depression and anxiety in patients with CD and should routinely screen for these conditions at the time of diagnosis, periods of active disease, and after IBD-related surgeries or hospitalizations.[65,73-75] Sleep disturbances, which are higher in patients with IBD and those with depression or anxiety, are associated with increased flares in patients with CD.[76] Effective treatment options for depression and anxiety, including pharmacotherapy and/or psychotherapy (eg, cognitive behavioral therapy),[65] may impact quality of life,[77] coping skills, and adherence to medications in patients with IBD.[78] Currently, there is a lack of convincing evidence to support whether interventions for depression and anxiety specifically alter disease course in IBD.[67,79,80] Overall, given the significant morbidity associated with these psychologic conditions, treatment should be administered when there is clinical suspicion or when screening tests are positive.

Exercise

Physical activity is reduced among patients with IBD.[81,82] In a retrospective analysis of 12,014 German employees, Sonnenberg found a lower prevalence of IBD among occupations requiring increased outdoor physical activity.[83] In patients with IBD, regular low-intensity exercise can reduce stress and depressive symptoms and improve quality of life and coping skills.[84-87]

Exercise has universal benefits for patients with IBD in reducing the risk of heart disease, stroke, diabetes, and cancer. IBD-specific benefits include improving bone mineral density,[88] psychologic health,[89,90] and joint health, especially in patients with ankylosing spondylitis.[90] Given the importance of exercise, additional studies are needed with larger sample sizes and longer, more intense periods of exercise to determine its direct effect on CD. Low-to-moderate–intensity exercise should be encouraged to improve functional capacity and quality of life and prevent a sedentary lifestyle.

Other Environmental Factors

Seasonal Variation

Given the relapsing and remitting nature of IBD, several researchers have suggested that seasonal variation may affect the onset and clinical course of IBD.[91-95] Auslander and colleagues collected information from the Clinical Outcomes Research Initiative database and were not able to discern any seasonal pattern variation of either IBD subtype.[96] Birth date studies are also conflicting.[97-102] Based on the current data, there is insufficient evidence to conclude that a seasonal variation in IBD onset or disease activity exists.

Appendectomy

Early appendectomy has been consistently shown to have a protective effect in UC in multiple studies,[10,103-105] although in CD the association is less well defined. In 2008, a systematic review found an increased risk of CD following appendectomy (relative risk, 1.61; 95% CI, 1.28-2.02).[106] In this analysis, significant heterogeneity existed among the studies, and the risk of CD was largely increased in the first year after appendectomy and was no longer significant after 5 years.[106] CD and acute appendicitis may present with a similar clinical presentation, and some of the association seen within the initial time period after appendectomy may be related to a diagnostic bias.[107] Given this uncertainty, clinicians must remain highly vigilant for an alternative diagnosis in patients who present with atypical appendicitis.

Summary

In spite of numerous studies, environmental risk factors have not fully explained the root cause of CD and may only partly contribute to disease pathogenesis. Early childhood factors still remain unclear, and further understanding of factors such as hygiene, breastfeeding, and diet on the intestinal microbiota will help elucidate the influence of these factors on the etiology of CD. The strongest environmental disease modifier thus far is cigarette smoking, and smoking cessation should be encouraged in all patients with CD. Among other lifestyle factors, high dietary intake of total fat, polyunsaturated fat, and meat was associated with increased risk of CD, and high fiber and fruit intake was protective of CD. Also, high perceived stress, sleep impairment, and ineffective coping mechanisms may play roles in exacerbation of disease. In general, patients should be routinely screened for depression and anxiety due to their high prevalence in IBD, and patients should be offered treatment if indicated. In addition, regular exercise should be encouraged because it can improve quality of life and emotional health. Currently, other than smoking, no specific environmental factors or infections have been clearly linked to the onset of CD. Future prospective studies are needed to better understand the effects of childhood hygiene, breastfeeding, air pollution, and diet on the onset and disease course of CD.

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