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TOPIC HIGHLIGHT

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Impact of environmental and dietary factors on the course of inflammatory bowel disease

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Abstract

Besides their possible effects on the development of inflammatory bowel disease (IBD), some environmental factors can modulate the clinical course of both ulcerative colitis (UC) and Crohn's disease (CD). This review is mainly devoted to describing the current knowledge of the impact of some of these factors on the outcome of IBD, with special emphasis on smoking and diet. Although the impact of smoking on the susceptibility to develop CD and UC is firmly established, its influence on the clinical course of both diseases is still debatable. In CD, active smoking is a risk factor for postoperative recurrence. Beyond this clinical setting, smoking cessation seems to be advantageous in those CD patients who were smokers at disease diagnosis, while smoking resumption may be of benefit in ex-smokers with resistant UC. The role of dietary habits on the development of IBD is far from being well established. Also, food intolerances are very frequent, but usually inconsistent among IBD patients, and therefore no general dietary recommendations can be made in these patients. In general, IBD patients should eat a diet as varied as possible. Regarding the possible therapeutic role of some dietary components in IBD, lessons should be drawn from the investigation of the primary therapeutic effect of enteral nutrition in CD. Low-fat diets seem to be particularly useful. Also, some lipid sources, such as olive oil, medium-chain triglycerides, and perhaps omega-3 fatty acids, might have a therapeutic effect. Fermentable fiber may have a role in preventing relapses in inactive UC.

Key words: Environmental factors; Dietary factors; Non-steroidal anti-inflammatory drugs; Smoking; Infections; Inflammatory bowel disease

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INTRODUCTION

Despite the advances in uncovering genetic risk for Crohn's disease (CD) and ulcerative colitis (UC) over the past decade, the etiopathogenesis of inflammatory bowel diseases (IBDs) cannot be explained only in terms of genetic susceptibility. In fact, a vast number of possible environmental risk factors for the development of IBD have

been investigated, including smoking, dietary factors, psychological stress, use of non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives, appendectomy, breastfeeding, as well as infections and other events related to the so-called "hygiene hypothesis" in childhood[1].

In addition to their putative effects on the development of IBD, some environmental factors can play a role in modulating the clinical course of both UC and CD. This review is mainly devoted to describing the current knowledge of the impact of some of these factors on the clinical outcome of IBD, with special emphasis on smoking and diet. The role of microbial factors (namely, the commensal microflora, and pathogens such as *Mycobacterium avium ssp*. paratuberculosis) in the pathogenesis of IBD will be not discussed.

SMOKING

Tobacco is the best established environmental factor affecting the susceptibility to develop IBD[2] and maybe its clinical course, with opposite effects in CD and UC. However, most of the published studies assessing the impact of smoking on the long-term clinical outcomes of IBD are retrospective, often leading to controversial results.

Role of smoking on the clinical course of CD

Beyond the higher incidence of CD among smokers, several studies suggest that continuing to smoke leads to worse clinical outcomes[3]. The underlying mechanisms of this deleterious effect are not well understood, but it has been reported that tobacco glycoprotein may be responsible for promoting a Th1 cell response[4]. Moreover, tobacco increases production of reactive oxygen species and impaired antioxidant capacity has been shown in smokers[5].

Smoking has been associated with a higher risk of relapse[6,7] and increased need for immunomodulators[8], but the strongest evidence of the deleterious effect of smoking upon the course of CD lies in the beneficial consequences of smoking cessation[9]. Cosnes *et al*[10] demonstrated that patients who stop smoking for at least 6 mo are at a lower risk of relapse in the following 12-18 mo, as compared to non-quitters.

The negative impact of active smoking may not be the same in all CD patients and it has been suggested that it may depend, at least, on gender and disease location. The effect of smoking has been reported to be more marked in women[8,10]. While the natural history of colonic CD seems to be the same in smokers and non-smokers, the rates of relapse[11] and intestinal resection are higher among smokers with ileal disease[6]. In addition, smoking has been associated with a lower prevalence of inflammatory (non-stricturing, non-penetrating) behavior of the disease, thus suggesting that tobacco facilitates progression towards complicated disease[12-14]. Nevertheless, this may only reflect a greater proportion of smokers among patients with ileal involvement[15].

The negative effects of tobacco seem to be dose-dependent, and some studies pointed to an increased risk of surgery and persistent inflammatory activity in those patients smoking over 10 cigarettes/d[12,16]. Conversely, a recent study reported non-detrimental effects of active smoking on CD course, but passive smokers needed immunosuppressants and infliximab more frequently than non-passive smokers[17]. Although seldom assessed, genetic background may also play a role, as suggested by the lack of association between smoking and CD in Jewish patients in Israel[18].

The worse clinical evolution among smokers might also be explained by a lesser response to drug therapies. Despite initial data suggesting a decreased likelihood of response to infliximab for luminal CD in smokers[19,20], larger studies failed to find any association between smoking and infliximab response[21-23]. We assessed the influence of smoking on the response to thiopurines in steroid-dependent IBD and, although no differences between smokers and non-smokers were found, CD responders who continued smoking had a higher rate of relapses during follow-up. Surprisingly, we found that smoking was an independent predictor for the need of thiopurine discontinuation because of side effects, leading to a lower treatment efficacy among CD patients (as compared to UC) when evaluated by intention-to-treat analysis[24].

Postsurgical recurrence is the clinical scenario in which active smoking has better proven to worsen CD prognosis both in the short- and long-term[25]. Smoking has been reported to be an independent risk factor for endoscopic, clinical, and surgical recurrence[26-28]. We have recently reported the results of the first prospective study assessing risk factors for endoscopic recurrence in a series of 152 CD patients undergoing ileo-colic resection[29]. Smoking was independently associated with significant postoperative recurrence as defined by the development of clinical recurrence and/or Rutgeerts grade 3 or 4 of endoscopic recurrence, whereas the only independent protective factor was the use of thiopurines[29]. Of interest, postoperative recurrence has been reported to be much more marked among heavy smokers (> 10 cigarettes/d)[26,29]. In spite of the fact that it has been suggested that the harmful effect of tobacco in CD might be neutralized by the use of immunomodulators[10], this does not seem to be the case in postoperative recurrence where two different studies identified both azathioprine use and active smoking as independent predictors for both endoscopic and surgical recurrence[26,29].

Role of smoking on the clinical course of UC

There is strong evidence pointing to a protective effect of tobacco on the susceptibility to develop UC[2]. Early studies, performed before the widespread use of calcineurinic drugs and infliximab, suggested higher rates of flares, hospitalizations, and even colectomy for UC among non-smokers[30-33], but these findings were not confirmed in most recent studies[34,35]. Conflicting results have been obtained about the effect of tobacco on retrograde progression of distal forms of UC[31,36-38].

Some authors reported a worsening in clinical out-

comes among UC patients who quit smoking[30,39], while improvement of disease activity has been noticed in ex-smokers who returned to smoke[40,41]. A number of trials show the efficacy of nicotine for inducing remission in active UC, although with a high rate of mild side effects[42]. In fact, some authors still propose "mild smoking" as an alternative therapy in patients with resistant UC[43].

DIET

Along with microbiota, dietary products are the most common luminal antigens in the bowel and may influence intestinal inflammation. Possible mechanisms include a direct antigenic effect, alteration of gene expression, modulation of inflammatory mediators (e.g., eicosanoids), changes in the composition of the enteric flora, and effects on gut permeability. Thus, the role of dietary habits on the development of IBD has been extensively investigated in case-control retrospective studies subject to different biases[44,45]. In a recent systematic review of these studies, high intakes of total fat, omega-6 fatty acids and meat were associated with increased risk of developing IBD, while high vegetable and fruit intake decreased the risk for these diseases[45]. A recent case-control study suggests that increased intake of refined sugars may facilitate the development of CD and UC[46]. Prospective studies are necessary to confirm the role of dietary factors on the development of IBD.

Role of diet on the clinical course of IBD

For decades, physicians based dietary counseling for IBD patients on restrictive criteria. This was because the so-called "bowel rest" was considered as a sine qua non to induce disease remission. However, controlled trials clearly demonstrated that drug-induced IBD remission was not influenced by the type of nutritional support (i.e., enteral, parenteral or oral conventional foods)[47-49]. Thus, the concept of "bowel rest" has been abandoned, and IBD patients are now advised to eat a diet as unrestricted as possible.

Food intolerance: Does it have a role in dietary management of IBD? IBD patients often complain of food intolerance. In a prospective study, 65% out of 130 patients who completed a food questionnaire reported to be intolerant to some food item, as compared to only 14% out of 70 healthy controls ($P < 0.0001$)[50]. A more recent study in 187 UC patients confirms these findings: 50% of patients avoided some foodstuff (mainly dairy foods, fruits and vegetables)[51]. However, 22% of patients ate supplemental amounts of these food items because they had the perception that these improved their symptoms[51].

Despite its high prevalence, food intolerance is quite inconsistent in IBD patients. Pearson *et al*[52] sequentially introduced single conventional foods in 28 CD patients who had gone into remission with an elemental diet. Twenty patients reported intolerance to some of these foods, but seven of them were tolerant to it after a re-challenge. Of interest, one patient who was also intolerant to this rechallenge, could tolerate the "offending" food after a second blinded rechallenge, and someone even had opposite responses to two blinded rechallenges with the same food item[52].

These data well illustrate how difficult it is to prove food intolerances in IBD patients. From this perspective, avoiding every food that causes patient's upset is an unwise strategy. In a large series of patients with inactive UC, dietary changes based on the patient's self-perceptions did not have any influence on the relapse rate[51]. Therefore, bearing in mind the fact that protein-energy malnutrition and other nutritional deficiencies are frequent in IBD, patients with UC or CD should be advised to avoid only those food items which repeatedly and systematically worsen their symptoms. In this setting, two groups of foods often raise concerns both among patients and doctors: dairy foods and dietary fiber.

None of the milk components has been proven to play a role in promoting bowel inflammation, causing the disease or triggering a flare. In contrast, it is well known that dairy foods are the main dietary source of calcium, which is necessary to prevent metabolic bone disease in these patients. However, it is also true that a significant proportion of healthy people (mainly in the Mediterranean basin) have lactase deficiency. Unabsorbed lactose reaching the colon may cause diarrhea and/or bloating in a dose-dependent manner. This phenomenon, which does not depend on the fact of suffering from IBD, may occur in lactase-deficient patients with these diseases, thus worsening their symptoms. Studies performed in our laboratory suggest that the prevalence of lactose malabsorption (as assessed by hydrogen breath test) is not higher in IBD patients than in healthy controls[53]. Therefore, IBD patients should not limit their milk intake during flares unless it clearly worsens diarrhea. Moreover, even in these cases, dairy foods with lower lactose contents (i.e., yogurt) may be well tolerated.

Prescribing a low-residue diet - that is, devoid of insoluble fiber - may be advisable during acute flares of IBD, particularly in patients with stricturing CD or severe UC attacks. Soluble fiber generates much less residue than insoluble fiber, and is fermented by colonic microflora yielding several products such as short-chain fatty acids (SCFA) - mainly butyrate - than can be of benefit in IBD. Butyrate is the preferred fuel for colonic epithelial cells. Decreased fecal levels of SCFA have been reported in patients with UC in relation to the severity of inflammation[54], and impaired beta-oxidation of butyrate could be demonstrated in patients with active and even inactive UC[55,56]. Experimental work suggests that butyrate is able to down-regulate the production of proinflammatory cytokines, and also nuclear factor kappa B (NF-κB) activation[57].

Soluble fiber may be particularly useful in inactive UC. In a randomized controlled trial, *Plantago ovata* husks (a source of slowly fermentable soluble fiber) were as

effective as mesalazine for preventing disease relapse in patients with quiescent UC[58]. In active UC, however, the use of soluble fiber might be potentially detrimental. The presence of intraluminal blood (and, hence, oxygen), and a lower intraluminal pH during active disease may favor the growth of lactic acid-producing bacteria (*Lactobacilli* and *Streptococci*). Lactic acid directly damages the bowel mucosa. Indeed, increased levels of fecal lactic acid have been reported in patients with active UC[59].

The usefulness of "exclusion diets" in CD has been supported by several authors due to their potential capacity to prevent clinical relapses and spare steroids. To date, only one prospective randomized controlled trial assessing the role of exclusion diet in preventing relapse in inactive CD has been published[60]. Seventy-eight patients, who had gone into remission with an elemental diet, were randomized to receive an exclusion diet (i.e., sequential introduction of foods, with exclusion of those that elicited symptoms) or prednisolone (40 mg/d, with tapering dose until discontinuation by week 12) (control group)[60]. Treatment of a control group is hard to justify, since it is well-known that steroids are not useful as maintenance therapy in CD. Anyway, the two-year cumulative probability of relapse was lower in the group treated with the exclusion diet than in the control group (62% *vs* 79%, $P = 0.048$)[60]. However, 62% is a high relapse rate, suggesting that exclusion diets benefit only a minority of CD patients.

Food components as primary treatment for CD: In the last three decades, the possibility that enteral nutrition could be used as primary treatment (i.e., able, *per se*, to induce remission) in active CD has been a matter of debate.

To date, four meta-analyses of the trials comparing enteral nutrition *vs* corticosteroids in active CD have been published[61-64]. All of them agree that steroids are better than enteral nutrition in inducing remission but they also indicate that, as a whole, enteral nutrition is able to induce remission in about 50%-60% of patients, a remission rate substantially higher than that obtained with placebo in active CD, which barely achieves 30%. This suggests that enteral nutrition (or, at least, some enteral formulas) would have a primary therapeutic effect in active CD (or, at least, in some subsets of patients). The primary therapeutic effect of enteral nutrition in CD is particularly relevant for children, as confirmed by two meta-analyses of pediatric trials which conclude that enteral nutrition is as effective as steroids in inducing remission in children[65,66]. In addition to its role in active CD, enteral nutrition is suggested to be useful for preventing relapse both in children[67] and adults[68]. Recent data suggest that it could also have a role in preventing postoperative recurrence[69].

The mechanisms whereby enteral nutrition exerts its primary therapeutic effect in CD remain obscure. The hypothesis that elemental (i.e., amino acid-based) diets would be particularly useful by virtue of their low antigenicity was challenged by the results of meta-analyses of randomized trials comparing elemental *vs* non-elemental (i.e., peptide- or whole protein-based) diets, which showed that both types of diets were equally effective in inducing remission[61,64].

To date, the amount and/or the type of dietary fat are major candidates for the therapeutic effect of enteral nutrition in CD. Recent meta-analysis suggests very low fat (i.e., less than 3 g/1000 kcal) diets could be particularly effective[64]. Early studies pointed out that olive oil-based diets were better that diets based on seed oils (corn, safflower, sunflower, soybean), suggesting that oleic acid would be better than linoleic acid in reducing inflammation[70]. Experimental data also support this view[71,72]. However, this hypothesis could not be confirmed in a trial comparing linoleic acid- and oleic acid-based diets, where the latter performed particularly badly[73]. As the oleic acid source in this trial was not olive oil but synthetic triolein, it cannot be ruled out that other components of olive oil (e.g., antioxidants) could exert anti-inflammatory actions in these patients.

Although coconut oil-derived medium-chain triglycerides (MCT) are traditionally considered as a mere easy-to-oxidize energy source, recent data support the idea that they can also exhibit immunomodulatory properties. In fact, there is growing experimental evidence that MCT are able to improve bowel damage both in spontaneous and induced animal models of intestinal inflammation[74-77]. There are also some clinical data suggesting that replacing part of dietary fat with MCT would contribute to the primary therapeutic effect of enteral nutrition in CD[78-80].

Surprisingly, fish oil-derived omega-3 fatty acids - the paradigm of anti-inflammatory lipids - have been scarcely assessed in the setting of enteral nutrition formulas for CD. Several randomized trials have been published, however, on the role of fish oil supplements as therapy for both active and inactive CD and UC, which have been systematically reviewed[81-83]. Overall, available data do not allow supporting the use of omega-3 fatty acid supplementation for the treatment of both active and inactive IBD. Negative results are quite consistent in trials assessing the use of omega-3 fatty acids to maintain disease remission, particularly UC, and to a lesser extent CD. Trials on their use in active disease do not allow us to draw firm conclusions, mainly because of the heterogeneity of their design (UC) or their small number (CD). In most trials, the appropriateness of the selected placebo is questionable[83].

NSAIDs

Since it is known that NSAIDs can induce gastrointestinal mucosal inflammation, it has been suggested that they might trigger disease exacerbation in IBD patients. Several potential mechanisms for this phenomenon have been proposed such as cycloxygenase (COX) inhibition, leukotriene shunting or inhibition of NF-κB activity, although none of them has been firmly demonstrated[84].

Most (but not all) retrospective, uncontrolled or cross-sectional studies evaluating the impact of NSAID use on IBD relapse agree on the potential deleterious effect of these drugs on quiescent IBD[84,85]. In the only prospective controlled study assessing disease relapse with the use of different NSAIDs as compared to acetaminophen in IBD patients without arthritic complaints, a significantly increased risk of relapse with NSAIDs was reported[86]. Interestingly, patients who tolerated NSAIDs for a week did not seem to be at risk for relapse, suggesting that drug-induced IBD flares occur early after starting NSAID use and only in a subset of susceptible patients. It is also still debated whether selective COX-2 inhibitors are safer than conventional NSAIDs for patients with IBD. The only prospective, randomized, double-blind, controlled trial performed to date showed no increase in UC flares as compared to placebo[87], but most authors conclude that further randomized, double-blind trials are needed to address this issue[84,85].

INTESTINAL INFECTIONS

Intestinal infections by enteropathogens have been associated with both IBD onset and IBD relapses, and stool microbiological studies are usually advised in patients with IBD flares. Several prospective and retrospective studies show that intestinal infections assessed by stool cultures occur in less than 10% of IBD flares, mainly in those patients with extensive colonic involvement[88-93]. However, the clinical relevance of such infections on IBD course has not been appropriately assessed, and no study has specifically addressed the effect of adding antibiotic therapy in patients with active IBD and a positive stool culture. Baliellas *et al*[89] reported that only half of the patients with active IBD and positive stool cultures achieved symptomatic remission after antibiotic therapy alone, despite stool cultures becoming negative in all of them.

Clostridium difficile infection (CDI) has become in recent years a worldwide epidemic phenomenon also affecting IBD patients. In the last two decades, the prevalence of CDI increased two-fold in UC and almost three-fold in CD[94]. As for enteropathogen intestinal infections, IBD patients with colonic involvement seem to be those at higher risk for CDI[95-97]. In addition to the risk factors for CDI in the general population, increasing age and steroid use seem to be particularly relevant in IBD patients, with no conclusive data about the role of other immunosuppressants[98]. Several studies have reported that CDI worsens IBD outcome, with higher rates of surgical procedures, longer hospital stay, and higher mortality, as compared to patients admitted to the hospital with IBD or CDI alone[94,95,97,99].

Finally, many studies have been published addressing the role of intestinal cytomegalovirus (CMV) infection in IBD, mainly in UC[100]. Two prospective studies demonstrated that this infection was a reactivation of CMV carriers that occurs almost exclusively in active, steroid-refractory UC patients[101,102]. However, the small number of patients included in both studies does not allow ascertaining whether CMV reactivation is the cause of refractoriness or the consequence of steroid use, and also whether it worsens UC outcome or if it is only an innocent bystander.

OTHER ENVIRONMENTAL FACTORS

Breastfeeding

Breastfeeding is a protective factor against several immunologically-based diseases. In fact, breast milk is relevant for acquiring tolerance against bacterial microflora and dietary antigens. Most studies investigating the role of breastfeeding on the development of either UC or CD have shown a protective effect, as concluded in a meta-analysis of 14 case-control studies published in 2004[103]. Subsequent studies confirmed these results (especially for those infants breastfed for more than six months)[46], while others suggest that breastfeeding could promote CD in childhood, rather than protecting from its development[104].

Obesity

IBD, particularly CD, has been traditionally associated with protein-energy malnutrition and other nutritional deficiencies. However, in recent years the prevalence of obesity among IBD patients has been increasing[105] in parallel with the obesity epidemics in the general population of developed countries. Case-control studies suggest that obese CD patients are more prone to perineal disease[106] and early surgical treatment[107].

Vaccinations

The role of vaccinations - mainly attenuated measles-containing vaccines - in the development of IBD is a matter of debate, with studies reporting a positive[108], negative[109] or no association[110,111] with IBD. A recent case-control study reported that vaccinations against pertussis and polio increase the odds of suffering IBD[46]. The exact role, if any, of vaccinations with regard to IBD is far from being elucidated.

Oral contraceptive pills

A meta-analysis conducted in 2008 showed that the use of oral contraceptives was associated with an increased risk of both CD and UC[112]. The risk increased with the time of exposure and reversed after pill discontinuation[112]. The effect of oral contraceptives on the risk of IBD appears to be related to estrogens. Estrogen acts as an immune enhancer and may increase the production of tumor necrosis factor by macrophages. Also, estrogen may induce microthrombotic phenomena in the bowel due to its thrombogenic potential.

Appendectomy

Appendectomy is associated with a lower risk of suffering from UC, particularly in children who are operated

before the age of 10, as shown in a meta-analysis of 17 case-control studies[113]. Investigations on the relationship between appendectomy and CD are less conclusive, in spite of the fact that a recent meta-analysis showed an increased risk of CD in appendectomized subjects[114]. However, this association was particularly strong for those appendectomies performed within one year before CD diagnosis, and almost null for those performed five years before CD[114], suggesting that this is a circumstantial rather than causative relationship.

Psychological stress

Psychological stress has been hypothesized to play a role both in the pathogenesis of IBD and as a triggering factor for disease relapse as well. However, retrospective observational studies have yielded conflicting results[115,116].

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