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EDITORIAL

Effect of smoking on inflammatory bowel disease: Is it disease or organ specific?

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Abstract

Smoking is an important environmental factor in inflammatory bowel disease (IBD) with differing effects in ulcerative colitis (UC) and Crohn's disease (CD). Never smoking and formerly smoking increase the risk of UC, whereas smoking exacerbates the course of CD. The potential mechanisms involved in this dual relationship are yet unknown. A reasonable assumption is that smoking has different effects on the small and large intestine. This assumption is based on animal and human studies that show that the effects of smoking/nicotine on CD and UC depend on the site of inflammation and not on the type of disease.

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INTRODUCTION

The relationship between smoking and inflammatory bowel diseases (IBD) is complex. Crohn's disease (CD) is associated, in some studies, with smoking. Smoking may also have detrimental effects on the clinical course of the disease. In contrast, ulcerative colitis (UC) is largely a disease of nonsmokers or former smokers.

In a large meta- analysis performed by Calkins[1] the association between smoking and CD was found to be consistent. The meta-analysis yielded a pooled odds ratio (OR) of 2.0 for smokers compared with nonsmokers to have CD and an OR of 1.8 for former smokers compared with nonsmokers. On the other hand, the meta-analysis reported a pooled OR 0.41 for current smokers compared with non-smokers to have UC.

In terms of the risk for recurrence or relapse, Cottone *et al*[2] found smoking to be an independent risk factor for the development of clinical (hazard ratio 1.46), surgical (hazard ratio, 2.0), or endoscopic recurrence (OR 2.2) in a group of 182 patients who underwent surgery for CD.

Cigarette smoking might even have beneficial effects on the course of UC. The exact mechanisms involved in the interaction of smoking and the course of IBD remain unclear.

Nicotine is assumed to be the active moiety of cigarettes. Some potential mechanisms involved in this dual relationship may include changes in humoral and cellular immunity, changes in cytokine and eicosanoid levels, gut motility, gut permeability, changes in blood flow, colonic mucus and oxygen free radicals. The differential therapeutic consequences in IBD include suggestions to stop smoking in CD patients and applying nicotine in different application forms for UC[3].

Many of the studies that compared the effect of smoking on CD do not focus on the effect of cigarette smoking on disease location. No epidemiologic study directly addressed the question of the effect of smoking in patients with isolated Crohn's colitis. Three clinical studies from Israel found no correlation between smoking and CD[4-6]. This led us to postulate that the opposite effects of smoking on CD and UC are a consequence of the site of inflammation (colon *vs* the small intestine) and not with the specific disease (CD *vs* UC).

DIFFERENTIAL EFFECTS OF SMOKING ON THE SMALL AND LARGE INTESTINE

Animal models

The effect of nicotine administration in animal models of gastrointestinal injury was first examined in the colon. Eliakim *et al*[7] have shown a biphasic effect of chronic nicotine treatment in a trinitrobenzene sulfonic acid (TNBS) induced colitis, a model with features mimicking CD. While lower doses (12.5-25 mg/L) were protective, higher doses (250 mg/L) were deleterious. The effects of nicotine on small intestinal inflammation have been less well characterized. Chronic nicotine administration

at the dose that was protective to the colon in both TNBS and iodoacetamide models that mimic CD (12.5 mg/L), aggravated jejunitis induced by iodoacetamide[8]. These same effects were later demonstrated in a model of jejunitis and colitis simulating CD in IL-10 knockout mice[9].

The divergent effects of nicotine in small bowel compared to colonic injury suggested that regional differences might exist between these organs regarding mechanisms of mucosal defense. In animal studies, interesting regional differences emerged: in the normal rat jejunum, chronic nicotine administration decreased PGE2 generation and increased NOS activity, but had no effect on the microcirculation; whereas microcirculation in the colon was enhanced, but NOS activity or PGE2 generation were not affected in the normal rat colon by nicotine administration[8].

In order to further assess the different effects of nicotine on the colon and small intestine, the authors studied the effects of nicotine administration on cytokine profile in small bowel, colonic mucosa and blood of normal rats. Acute nicotine administration (1 or 2 d) significantly decreased jejunal IL-2 and IL-10 levels and increased IL-6 levels, while chronic administration (7 d) caused an increase in IL-6 and a decrease in IL-10 levels[10]. On the other hand, colonic mucosa IL-2 levels decreased significantly, with no change in IL-6 or IL-10 mucosal levels. Thus, the colonic cytokine profile behaved totally differently to nicotine exposure compared to small bowel mucosa. Nicotine administration decreased the anti-inflammatory mediator IL-10 levels in the small bowel and increased the level of the pro-inflammatory mediator IL-6, possibly contributing to mucosal damage in that region. Nicotine decreased the levels of the pro-inflammatory mediator IL-2 in colonic mucosa. Similar effects of smoking have been found for the pro-inflammatory mediators IL-8 and IL-1beta in human colonic mucosa. Smokers with IBD had a significant reduction in cytokine levels, specifically IL-1beta and IL-8 in patients with UC and IL-8 in patients with CD[11].

Furthermore, nicotine administration significantly increased both somatostatin and intestinal trefoil factor mRNA expression in the colon but not in the jejunum of IL-10 knockout mice[9].

Human population studies

Most studies that focus on the relationship between smoking with IBD do not differentiate between the effect of smoking on disease behavior and location in CD. Few studies have reported the effects of cigarette smoking on different locations of CD in the GI tract. Bridger *et al*[12] found that males who smoked had higher prevalence of small bowel disease (OR, 3.68). Moreover, smoking appeared to protect against colonic disease (OR, 0.27).

Lindberg *et al*[13] studied the effect of smoking on the localization and clinical course of 231 patients with Crohn's disease. Heavy smokers (greater than 10 cigarettes/d) had small bowel CD more often than patients that smoked less than 10 cigarettes/d ($P = 0.045$). Brant *et al*[14] performed a multicenter retrospective record analysis of 275 unrelated patients with CD and found that smoking was a risk factor for ileal disease (O.R. 2.25 per pack per day at diagnosis), that was independent of the ileal risk from the mutant NOD2 genotype. Smoking was also a risk factor for time to surgery in ileal, but not colonic CD. Bustamante *et al*[15] studied a total of 161 IBD patients. Patients with CD were divided into those with or without colonic involvement. They evaluated the relationship between smoking and the type of IBD and its localization (colonic or non-colonic). Smoking was found to be more prevalent in patients with CD than with UC (72.8% *vs* 31.9%). Among patients with CD, smoking was more prevalent in patients with non-colonic involvement (84.6% *vs* 64.2%).

The largest study that dealt with the effect of smoking on IBD was conducted by the European Collaborative IBD Study. The aim of the study was to compare the clinical features at diagnosis and during the first year of follow-up in smokers and nonsmokers with IBD[16]. In this European, 19 centers prospective study 457 patients with newly diagnosed Crohn's disease and 930 with ulcerative colitis were included. The treating physician, using a standard protocol, recorded disease characteristics at time of diagnosis. Treatment characteristics were assessed after 1 year of follow-up. CD Patients who smoked were less likely to have colonic involvement ($P < 0.01$) and more often prescribed immunosuppressive medication ($P < 0.02$), suggesting that smoking protects the colon from inflammation.

CONCLUSION

No single explanation for the different effects of smoking on CD and UC has been identified. Reasonable assumptions for the differences in the effects of smoking between CD and UC, are disease location (esophagus to rectum *versus* colon), extent of bowel wall involved (transmural *versus* mucosal), genetic alterations (NOD2, IL-10), or the host's response to luminal bacteria.

In the current review, we summarize the data from animal and human studies showing that the different effects of smoking/nicotine on CD and UC depend on the site of inflammation and not on the type of disease. Further studies with larger patient populations are needed to clarify this issue.

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