Cigarette smoking and its relationship to inflammatory bowel disease: a review

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Introduction

Inflammatory bowel disease (IBD) is an all embracing term for the idiopathic chronic inflammatory conditions of the intestine, Crohn's disease (CD) and ulcerative colitis (UC)[1]. Both can affect any age group but usually present in young adult patients. UC affects 40-80 people per 100 000 in the West and its incidence is static, whereas the incidence of CD is 20-40 per 100 000 and on the increase.

The cause of both diseases is unknown and both tend to be of a remitting and relapsing nature. However, whilst UC is a mucosal disease affecting only the colon or part of it; CD causes trans-mural inflammation which can affect any segment of the gastrointestinal tract from mouth to anus with the terminal ileum being the region most commonly involved[1]. They seem to be two truly distinct conditions and one of the most intriguing differences between them is their different relationships to smoking habit.

Ulcerative colitis

That a relationship existed between UC and smoking habit was first reported by Samuelsson in 1976[2]. He found that patients with UC were significantly more often non-smokers than matched controls from the general population, but the significance of his observations remained largely unrecognized until Harries *et al.*[3] repeated this observation in 1982. Using a questionnaire survey of 230 patients with UC and 192 patients with Crohn's disease they showed that patients with UC were much less likely to be smokers than either controls, taken from patients attending a fracture clinic, or patients with CD. Since then this relationship has been studied in some detail by other workers and this finding repeatedly confirmed[4-23]. It now seems beyond doubt that a relationship truly exists[12] and that non-smokers have a relative risk of developing UC ranging between 0.17 and 0.96[6,8-11] in different studies. There is also evidence that the effect is dose related[6,8], with the relative risk for those who smoke >25 cigarettes per day being 0.1-0.2[6]. Whether sex differences exist is less clear. Some studies have shown the association to be greater in women who are current smokers[10] whilst other studies have failed to show a significant sex difference[11,13].

When the question of previous smoking habit is considered the relationship between UC and smoking seems to be even stronger. A number of studies have suggested that smoking has a protective effect against the development of UC with a rebound effect if you give up before the development of the disease. Motley *et al.*[24] showed that 52% of patients with UC developed the disease within 3 years of stopping smoking. Another study demonstrated that giving up from being a heavy smoker increased your relative risk of developing the disease by as much as 4.4[8]. In addition being an ex-smoker has been shown to have a detrimental effect on the clinical course of the disease as measured by number of hospitalizations or colectomy rate[25].

More problematical is the question of whether smoking might actually confer some advantage to a patient who has already developed ulcerative colitis. Following the early reports of the association between UC and smoking, de Castella[26] was the first to suggest that this might have therapeutic implications and cited a case in which relapses of UC seemed linked with attempts to give up smoking. Rudra *et al.*[27] contacted 30 patients with UC who had restarted smoking after giving up and half of these found that it appeared to improve their colitis. In a larger study of 209 patients with UC[25], disease severity was assessed using the two criteria of hospitalization and colectomy rate and although hospitalization rate was less in smokers than non-smokers the colectomy rate was similar. A significant finding was the 17.9-fold increased risk of colectomy in ex-heavy smokers again suggesting a rebound effect.

Crohn's disease

In contrast with UC, there is less known about the role of smoking in CD[6,8,10,11,15,16,28-30]. The classic study by Harries *et al.*[3] which first clearly demonstrated the relationship between smoking and UC, failed to show such a relationship for CD perhaps because the controls were not age and sex matched to the CD group only to the group with UC. When an age and sex matched case control study was performed using controls from a general practitioner's list[30], then the patients with CD were found to be more likely to be smokers than the controls, and were shown to have a relative risk of 4.8 compared with non-smokers for smoking habit before and up to the onset of the disease and 3.5 for current smoking habit. This was subsequently supported in a study by Silverstein *et al.*[29] when a group of 115 CD patients were found to be more likely to smoke at the time of symptom onset than were a group of 109 control patients with irritable bowel syndrome ('relative risk' 3.7). Further support comes from a case control study[6] with 109 cases of CD, with age and sex matched controls, which found that not only were smokers at greater risk of developing CD, with a mean relative risk of 4.0, but also the heavier the smoker the higher the risk, suggesting dose dependency. However, in a similar study performed

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with 144 CD patients smoking was found to double the relative risk but there was no added risk in heavy smokers[8]. More information comes from another case control study in Sweden in which 184 patients with CD were asked about current and previous smoking habit as well as previous tobacco smoke exposure when aged 0-15 years. This study confirmed the findings of an increased risk in smokers with the relative risk being 1.5 for men and 5.0 for women and also interestingly suggested that the relative risks of developing CD were 1.16 for men and 2.5 for women if they had been subjected to regular passive smoking as a child[10]. The sex difference noted in this study was also found in three other studies[6,11,30], although to a lesser extent.

It has also been suggested that relapses of CD may be related to smoking habit. When Sutherland *et al.*[31] studied recurrence of the disease, defined as the need for further surgery, in 174 patients he found that 5- and 10-year recurrence rates were significantly higher in smokers with the relative risk at 5 years being 2.2[31]. In a study by Holdstock *et al.*[5] smokers with Crohn's colitis tended to have more relapses and more pain than non-smokers and smokers with small bowel Crohn's disease tended to have more frequent bowel movements, more admissions to hospital, more operations, and higher white cell counts. Duffy *et al.*[32] found that current smokers experienced a relapse rate 1.6 times that of non-smokers. The therapeutic value of stopping smoking for individual patients with CD has been less clearly studied than the converse situation in UC and paradoxically it has also been stated that patients with CD are less likely to give up smoking than controls[29], possibly because of psychological factors associated with the disease.

Possible mechanisms

Attempts at explaining the undoubted association between IBD and smoking habit in terms of underlying pathophysiological mechanisms have been made difficult by the fact that the aetiology of both UC and CD remains unknown. The following mechanisms have, however, been suggested, although none is entirely satisfactory.

(1) Changes in the permeability of the intestine to harmful substances has been suggested as a possible cause for IBD[33,34]. Intestinal permeability as measured using the oral tracer ^{51}Cr-ethylenediaminetetraacetic acid is either normal[34] or increased[33] in UC. Prytz *et al.*[35] showed that intestinal permeability measured using this technique was decreased in smokers and suggested that this might explain the protective effect of smoking in UC. However Bjarnason *et al.*[34] showed that permeability was also increased in patients with small bowel CD using the same tracer so confusing the issue.

(2) Immunosuppression is a recognized method of treating IBD and smoking has been shown to alter both cellular and humoral immunity. In heavy smokers IgG, IgM and IgA levels are reduced, but IgE levels are increased[36]. Heavy smoking also induces a reduction of the ratio of T-helper-inducer to T-suppressor cells, thus acting in a similar fashion to immunosuppressive drugs[37]. If smoking exerts a protective effect in UC by causing immunosuppression this does not, however, explain why smoking is positively correlated with CD.

(3) Mucus is an essential component contributing to intestinal mucosal defence and it has been shown that colonic mucus in patients with UC is qualitatively and quantitatively abnormal[38]. It has also been shown that when colitic patients smoke the quantity of colonic mucus produced is returned to normal[39] and this may be a factor in protecting against the development of UC. Colonic mucus is, however, normal in CD[38] and this cannot explain the differential effects of smoking on the two diseases.

(4) A tendency to arterial thrombosis is associated with both inflammatory bowel disease[40] and smoking[41] and multi-focal gastrointestinal infarction has recently been demonstrated in CD and been proposed as a possible pathogenic mechanism[42]. Several effects of smoking contribute to the production of a prothrombotic state. Smoking is capable of causing endothelial cell damage[43] and directly inhibiting vascular prostacyclin (PGI_2) (an important vasodilator and inhibitor of platelet aggregation) synthesis[41] at the cyclooxygenase level. In addition smoking elevates plasma fibrinogen levels[44], increases plasma viscosity, increases packed cell volume[45], and decreases the level of both plasminogen and tissue plasminogen activator[46]. As well as these effects on coagulation it has been demonstrated that there is a reduction in rectal wall blood flow during smoking[47] which lasts up to 30 min. This combination of decreased flow and hypercoaguability may lead to an increase in the number of micro-thromboses that occur in CD and hence to exacerbations of the condition. It cannot, however, explain the protective effect of smoking on UC.

Conclusions

The opposing effects of smoking habit on the occurrence and subsequent course of UC and CD is intriguing and currently unexplained. That the association is definite seems, however, beyond dispute. Currently, because of its many other harmful effects, it would be difficult to justify recommending that a patient with UC should start smoking but a strong case could be made for advising smoking patients with CD to give up. It may well be that for any final explanation of this undoubted association we must wait for the true cause of these diseases to be discovered but it could also be that by further investigation of this association we will learn more about the mechanisms underlying IBD as a whole.

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