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Association of Smoking and Crohn's Disease: An Update

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Abstract

The relationship between smoking and inflammatory bowel disease (IBD), which has been widely studied for years, is complex and different in Crohn's disease (CD) and ulcerative colitis (UC). The negative effect on CD, not only on disease progression and post-surgical recurrence, but also on post-surgical complications after intestinal resection, on its influence on the reservoir and on the modification of the natural evolution of CD towards fistulizing and stenosing forms, makes a proper approach to the problem imperative. With the rise of biologics, the influence of smoking on the response to these drugs has been studied. Although some studies have found a worse response to these treatments in patients who smoke, it is unclear whether the response to biologics worsens, or whether it is simply a worsening of the underlying disease with a consequent reduced response to the drugs used. Furthermore, regarding the safety of biologics and small molecule drugs in smokers, smoking may worsen adherence to these treatments, increase their adverse effects and contribute to an increased risk of thrombosis in patients with Janus-kinase (JAK) inhibitors. Because of its high preventable morbidity and mortality, it is essential that patients with CD stop smoking. Patients should be informed by their physician and governmental strategies should be promoted to facilitate both cessation and to reduce the risk of relapse.

Keywords: Cancer, Crohn's Disease, Inflammatory bowel disease, Tobacco

Introduction

Inflammatory bowel disease (IBD) groups together a series of chronic disorders secondary to the interaction between genes, microbiota, environment and an excessive immune response that produces lesions of varying depth and extent in the intestine. It presents periods of increased and decreased inflammatory activity and its prognosis is conditioned by chronicity. There are two main entities: Crohn's disease (CD), ulcerative colitis (UC) and unclassified or indeterminate colitis. CD is transmural, which can lead to strictures, fistulas, and asbcesses. Lesions are usually patchy and can affect any part of the gastrointestinal tract. UC affects the mucosa of the rectum and continuously with variable extension to the rest of the colon. A minority of cases do not allow a definitive diagnosis of CD or UC to be established. We speak of colitis pending classification, and if after analyzing the histological characteristics of the colectomy specimen it is not possible to make a precise diagnosis due to overlapping characteristics between CD and UC, of indeterminate colitis [1-3].

Like other autoimmune and allergic diseases in developed countries, IBD has increased its incidence rates, and therefore its prevalence, to between 1 in 200 and 1 in 300 inhabitants in these countries. In Spain, the incidence is similar to other European countries: 5-12 cases of UC/100,000 inhabitants/year and 3.5/9.5 cases of CD/100,000 inhabitants/year [4,5].

The link between smoking and IBD has been suggested for a long time but is now more clearly established. However, smoking has a different effect on patients with CD and UC. In CD, smoking acts both as a risk factor for developing the disease and as a risk factor for a more aggressive disease course in patients already diagnosed. In fact, CD is more common in active smokers than in non-smokers [6,7]. Numerous prospective studies have demonstrated a detrimental effect of smoking in this disease [8,9]. In contrast, in UC, the evidence seems to indicate that smoking may play a protective role, not only in the development of the disease, but also in the prevention of flare-ups, less need for surgery and use of immunosuppressants [10,11]. Smoker patients have a higher

risk of developing CD compared to never smokers (OR, 1.76; 95% CI, 1.40-2.22) and a lower risk of developing UC compared to never smokers (OR, 0.58; 95% CI, 0.45-0.75) [6,7].

Influence on the Course of Crohn's Disease

Patients with CD who smoke are at higher risk of complications, relapses and the need for surgery [12] (**Table 1**). This has been known previously for decades [13]. The effect of smoking also appears to be dose-dependent [14] and to have a greater influence on the female sex [15], in part because women are more dependent on nicotine, which makes it more difficult for them to quit smoking [16]. Recently, a multicentre retrospective study aimed to identify predictors of disabling Crohn's disease with the intention of offering an early approach to patients with poorer prognosis. Patients with uncomplicated Crohn's disease (inflammatory pattern and no perianal disease) were selected and smoking was identified as a risk factor for disabling Crohn's disease in these patients (OR = 2.09, 95% CI = 1.03 - 4.27) [17]. A meta-analysis published in 2016 that evaluated 33 cohort studies with 11,000 CD patients found that smokers had a 56-85% increase in disease flares over non-smokers [18].

Regarding the risk of undergoing surgery, some studies have shown that smokers have a 29% increased risk of surgery when compared to non-smokers [19]. Smoking increases the risk of surgery, re-resection rates [20] and post-surgical complications after ileocecal resection [21]. Smoking has also been associated with an increased risk of perianal surgery in patients with CD without biological therapy. Interestingly, this same study showed that in patients with moderate-severe Crohn's disease who were on treatment with biologics, smoking did not significantly increase the risk of luminal surgery, which may suggest a protective role of biologics versus smoking in the need for surgery [22].

A systematic review and meta-analysis evaluating risk factors associated with the development of Crohn's disease in the reservoir after ileo-anal anastomosis in patients with UC identified, among other risk factors, previous smoking (OR 1.80; 95% CI 1.35-2.39; $p < 0.0001$; I2 0%) as a risk factor for this entity. This should be taken into account for planning and preoperative as well as for prognosis after surgery [23]. Despite the protective role of smoking in UC, smoking has not been shown to exert the same effect on the reservoir and increase the risk of pouchitis in patients who quit smoking [24,25]. In addition, the response to dilatation of strictures secondary to CD and the need for further dilatation sessions or surgery increases in smokers [26].

In patients with CD and active smoking, progression to complicated forms of the disease (stenosing or fistulizing) has also been described [27,28]. This ability of smoking to alter the natural course of the disease was also demonstrated in a Spanish study published in 2013 where smoking patients had a higher risk of perianal disease (29.5% vs. 26.2% $P < 0.05$) and progression to stenosing disease [29]. The ileal location, the most common site in CD patients, seems to be affected even more likely in smokers, although these differences in site and also in CD behavior were small [30,31]. Regarding the influence of tobacco on extraintestinal manifestations, in

Table 1. Effects of smoking on the course and prognosis of Crohn's disease

Increased risk of clinical relapse/inflammatory flare-ups
Increased hospitalization rate
Increased need for surgery
Increased risk of post-surgical complications
Increased need for corticosteroids
Increased need for immunosuppressants
Poorer response to endoscopic dilatation
Increased frequency of progression to more complex forms (penetrating and stenosing)
Increased risk of perianal disease
Increased risk of surgery related to perianal disease
Increased severity/intensity of abdominal pain
Increased risk of MEIs (except PSC)
Increased risk of Crohn's disease in ileo-anal reservoir
Increased risk of Crohn's disease in offspring exposed to passive smoking during pregnancy and childhood
Increased risk of associated colorectal neoplasia (CRC) and colorectal cancer (CRC)
Reduced quality of life

a study conducted to identify clinical, serological and genetic factors associated with extraintestinal manifestations (EIMs) of inflammatory bowel disease, smoking was found to increase the risk of EIMs, with the exception of primary sclerosing cholangitis, where it exerted a "protective" effect [32].

Although initially the published studies did not appear to attribute an increased risk of IBD to children of smoking mothers or to passive smoking in childhood [33], recent studies relate early life exposure to tobacco to an increased risk of CD. The first one demonstrated how early life exposure to tobacco increased the risk of CD by 18% in adult offspring compared to those without early exposure (hazard ratio [HR] = 1.18, 95% confidence interval [CI] = 1.01–1.39) [34]. A second, prospective study showed that the risk of developing IBD in children exposed to maternal smoking during pregnancy or the first year of life depended on the level of smoking to which the children had been exposed. High exposure (mean ≥ 6 cigarettes/day) demonstrated a significant increased risk while lower exposure was not significant [35].

Finally, smoking in CD patients also has economic and quality of life implications. A Danish study showed, on the one hand, how the economic cost is much higher in smokers with CD compared to non-smokers with CD - there was no difference in the case of UC between smokers and non-smokers. On the other hand, it showed a decrease in quality of life in both CD and UC in smokers compared to non-smokers [36].

Cancer and Smoking

The influence of smoking on the risk of colorectal neoplasia in patients with IBD has also been studied. Although previous studies yielded conflicting results, a study published in 2023 showed that the higher the number of pack-years of smoking was associated with an increased risk of recurrent colorectal neoplasia in patients with IBD, independently of other established risk factors such as endoscopic inflammation. Smoking status, regardless of the amount of smoking, was not associated with this increased risk [37]. Therefore, based on the results of the presented study, smoking cessation should be recommended to all IBD patients to reduce the risk of colorectal neoplasia. Further studies should take into account other concomitant risk factors for colorectal neoplasia such as alcohol or diet [38].

Pathophysiology

Regulatory agencies have recognized the main chemical components of tobacco as hazardous to human health because of their high toxicity and increased risk of cancer [39]. The chemical composition of tobacco includes nitrosamines, polycyclic aromatic hydrocarbons, aldehydes, nicotine, phenols, carbon monoxides, radioactive elements and heavy metal ions, as well as carcinogenic substances [40]. Multiple hypotheses have been postulated to explain the dual effect of tobacco on IBD [41]. Substances such as nicotine and an increase in reactive oxygen species together with a decrease in antioxidant substances are believed to be behind the harmful effect of tobacco on this disease [42]. However, there is evidence to support a protective role for nicotine in UC mediated by activation of an anti-inflammatory cholinergic pathway that requires the α7 nicotinic acetylcholine receptor (α7nAChR) on immune cells [43]. In relation to the main inflammatory pathways involved in the pathophysiology of CD (T helper (Th)1/17 response), smoking appears to increase cytokine expression and immune cell recruitment, promoting autophagy and apoptosis [44]. Importantly, the effect of smoking on IBD is strongly modified by genetic and ethnic factors [45]. In addition to genetics, epigenetic risk factors for CD and UC have been identified. A recent publication demonstrated how DNA methylation at the DNMT3A, AHRR, LTA/TNF loci mediated the effect of tobacco on the pathophysiology of IBD [46]. Although there are epigenetic mechanisms common to CD and UC, the different impact of smoking between the two entities can be explained by unique epigenetic changes, such as MGAT3 hypomethylation associated with a more severe course in UC alone, or IER3 hypomethylation with a worse course in CD [47]. The importance of epigenetics in the field of IBD has been previously described through mechanisms such as histone modification, DNA methylation and telomere shortening [48]. It has also been shown that smoking can produce pro-inflammatory epigenetic changes at the level of adipose tissue stem cells, decreasing their anti-inflammatory and T and B cell proliferation inhibitory capacities [49]. Finally, the association between smoking and microbiota has also been described. Smoking cessation produces an early change in the gut microbiota that could interact with the immune response and explain the effect of smoking cessation with UC [50,51].

Post-surgical Recurrence in CD

Given the chronic nature of the disease, post-surgical recurrence is almost always the norm in CD patients after curative ileal or ileocolic resection. Without preventive treatment, endoscopic recurrence at one year after treatment is about 75% [52], both endoscopic, clinical and surgical [53].

In a recent study evaluating clinical predictors of early and late endoscopic recurrence after ileocolic resection in patients with Crohn's disease confirmed the involvement of smoking after surgery as a risk factor for endoscopic recurrence (OR = 2.78, 95% CI 1.16 - 6.67) [54]. Other studies, however, have linked active smoking to surgical (OR = 1.73; 95% CI, 1.17 - 2.53) but not endoscopic recurrence. In smokers, as in non-smokers, prophylactic treatment with biologic drugs after surgery was effective in reducing the rate of surgical and endoscopic recurrence [55]. Moreover, recurrence is more common in ileal resections, the site where the harmful effect of smoking

seems to be strongest. This post-surgical recurrence, as with the worse course, is greater with higher smoking - a dose-dependent effect [53]. Despite prevention of recurrence with immunomodulators and/or biologics after curative surgery, active smoking implies a more severe course, with an increased need for these drugs compared to non-smokers [56].

Influence of Tobacco on Treatments

The emergence of biologic drugs has been an unprecedented revolution in IBD. Their early use in patients with CD has made it possible to modify the course of the disease and reduce the need for admissions and surgery in these patients. The increased need for immunosuppressors and corticosteroids in smokers with CD has previously been demonstrated [15]. However, there is also a greater need for biologic drugs in these patients, probably reflecting the worse disease course linked to smoking [56].

Regarding whether smoking worsens the response to medical treatments, two meta-analyses presented contradictory results [57,58]. However, a prospective multicentre UK study seems to support a negative association between smoking and non-response to anti-TNF drugs [59]. The current published evidence does not clarify the impact of smoking on the efficacy of anti-TNF drugs in IBD [60].

The influence of smoking on the need for sequencing of various biologics in patients with CD has also been evaluated. A cohort of 281 patients was selected from a prospective database and classified according to their exposure to tobacco (smokers, ex-smokers and never smokers). The number of biologics used in each group was then analyzed, categorized into 3 groups: 0, 1, or ≥ 2 biologics. Current or former smokers were not found to sequence through more biologics when compared with never smokers. However, the researchers did not stratify the risk according to the amount of tobacco exposure [61]. In addition to the poorer response to anti-TNF drugs in smokers with CD, active smoking has also been associated with an increase in adverse effects in patients on biologic therapy. In particular, an increase in dermatological manifestations in CD and UC and arthralgias in CD patients was described [62].

It is important to pay special attention to the new JAK kinase inhibitor drugs approved for IBD because of their increased risk of thrombotic events, especially in patients with other associated prothrombotic risk factors. To study the effectiveness and safety of Tofacitinib, in smoking patients, a post hoc analysis of pivotal studies was performed [63]. Although the effectiveness and safety of the drug was generally similar in smokers/ex-smokers vs. never smokers, serious adverse events and infections were more frequent in the group of patients who had ever been exposed to tobacco than in never smokers. The risk of arterial or venous thromboembolism was similar in both groups: 1% in smokers/ex-smokers vs. 0.9% in never smokers.

Finally, in a Spanish study carried out to find out the prevalence of non-adherence to treatment in IBD patients and identify risk factors, showed that being a smoker was associated with low adherence (OR: 3.47; 95% CI: 1.36-8.90; P<0.01) [64].

Cessation of Smoking

Difficulty in quitting smoking is often determined by the influence of nicotine on the mesolimbic system. Nicotine administration increases dopamine levels through increased activation of dopaminergic neurons, thus activating reward systems, which ultimately leads to addiction [65].

The expansion of public health campaigns to reduce smoking has gradually reduced tobacco consumption in developed countries. However, less progress has been made in less affluent countries. Among the strategies used by governments are increased tobacco taxes, bans on tobacco advertising and promotion, prominent warning labels, bans on smoking in public, and educational and media efforts [65].

It must be taken into account that active smoking is a major determinant of preventable morbidity and mortality worldwide, and the only modifiable environmental factor clearly related to the appearance of Crohn's disease [30].

A population-based study assessing the risk of overall mortality based on smoking in patients with IBD found that a significant proportion of patients continued to smoke after diagnosis of the disease. Furthermore, the same study showed that smoking cessation at diagnosis was associated with a significant reduction in mortality compared to patients who continued to smoke after diagnosis [66]. In an international online survey of more than 1000 IBD patients, up to 77% reported ever smoking or using alternative tobacco products. About two-thirds of patients reported stopping smoking but subsequently relapsing, with a higher proportion in UC patients, highlighting the importance of increasing efforts to encourage smoking cessation in these patients [67]. In this sense, some studies have been carried out on the ability of a doctor in his office to get patients to quit smoking. A systematic review published in 2013 showed that a brief intervention in the consultation has a very small effect (an increase of between 1-3%) in achieving smoking cessation, and subsequent consultations and interventions only slightly increased the quit rate [68].

It seems, therefore, that the advice that a gastroenterologist can give in the consultation to promote smoking cessation may often not be enough to achieve adequate results. However, in a multicenter and prospective Spanish study carried out in 2013 in patients with CD, it was shown that education and advice

on smoking cessation, without the need for pharmacological therapy, is effective in patients with CD. Up to 88% of patients attempted to quit smoking after explaining the risks derived from smoking in their illness [69].

Once abstinence has been achieved, it is essential to minimize the risk of relapse. In this regard, relapse has been studied as being more frequent in patients with CD (46%) than in patients with UC (24%), (p = 0.029) being the average time to first relapse between 12-15 months [70].

Finally, the last few decades have seen a global expansion in e-cigarette use. The use of nicotine containing e-cigarettes on disease outcomes in CD or UC has not been well defined. A study was published in 2023 whose primary objective was to assess the effect of e-cigarettes on the need for initiation or change of biologic, hospital admission or surgery at 2 years. Although the authors recommend discouraging patients from initiating vaping because of its overall adverse health effects, e-cigarette use was not associated with worse outcomes among IBD patients [71].

Conclusion

Therefore, and to conclude, even in the era of biologics and new therapies, it is essential to quit smoking due to the very negative consequences it has on IBD. Patients must be informed and motivated to stop and the role of the gastroenterologist in the consultation is important. We must consider active smoking as a poor prognostic factor when monitoring patients, especially in post-surgical recurrence. Regarding the choice of treatments, it is not clear whether the response to biological drugs worsens, or it is simply a worsening of the underlying disease with a consequent reduction of the response to the drugs used. Passive tobacco exposure should also be avoided in the offspring of IBD patients for primary prevention of the disease [72].

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