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Symptomatic Effects of Smoking in Ulcertive Colitis: A Clinical Dilemma

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Abstract

Inflammatory Bowel Disease (IBD) is a digestive tract disorder manifesting mainly in two forms, namely Crohn's disease (inflammation of digestive tract) and ulcerative colitits (inflammation of large intestine lining). Genetic and environmental factors could potentially predispose towards IBD. From a smoking perspective, ulcerative colitis is frequently observed in ex-smokers of non-smokers whereas Crohn's disease is frequently observed among smokers. Smoking was reported to have distinct effects in these two types of disorders, nevertheless elicitation of humoral and cellular immunity was observed to be common in both the types of IBDs. Smoking has been implicated in disease amelioration in case of UC. However, smoking has been associated with several adverse effects including cardiovascular disease and carcinogenesis which outweigh the beneficial aspects. The present review collates information on the role of smoking in UC based on latest research outcomes and elucidates the effect of nicotine (an active constituent in smoking) and associated mechanism of action in IBD condition. Genetic and environmental factors are the cause of disorders like inflammatory bowel diseases (IBD). Ulcerative Colitis (UC) is a type of IBD which is mostly seen in non-smokers or former smokers. In UC protective effect of smoking is seen due to nicotine presence. While in Crohn's Disease (CD) smoking show opposite effects hence, it is complex to know relationship between IBD's. Humoral and cellular immunity changes are indulged in the relationship of both the IBD's. Therapeutically, nicotine is used for many diseases like ulcerative colitis, Alzheimer's disease, Parkinson's disease, Tourette's syndrome, sleep apnea, and attention deficit disorder. In case of active UC nicotine is effective while in most cases this nicotine becomes harmful and causes side effects like nausea, headache, dermatitis etc. Smoking is linked to most hazardous effects like atherosclerosis, pulmonary hypertension, cardiovascular diseases, carcinogenic disorders which make patients to quit smoking. This sudden ceasing of smoking may potentially elevate symptoms. Correlating with the previous data here we will compare effect of smoking based on genetic susceptibility, twins, gender, and smokers and non- smokers. Data is highly contradictory while the involved mechanism in both the cases is still unknown. In this paper we have mainly focused on smoking role in Ulcerative colitis (UC) depending on many studies done in recent years and also the effect and mechanism of nicotine action on our body.

Keywords: Inflammatory bowel diseases; Ulcerative colitis; Nicotine; Smoking

Introduction

Environmental and genetic factors can cause chronic disorders like inflammatory bowel disease [1-3]. Genetically, immunologically and histopathologically heterogeneous group of inflammatory bowel diseases is signified by the term IBD [4]. IBD showed significant increase worldwide in last few years. Environmental factors like diet, smoking, drugs (i.e., antibiotics), and lifestyle alterations are the most probable reasons for this phenomenon [4,5]. Study of many years showed smoking cigarette as a risk factor for developing IBDs [6]. A puff of cigarette consist of more than 4000 chemicals like aldehydes, quinones, benzopyrene, epoxides, and peroxides which is the risk factor for the development of many diseases such as atherosclerosis, pulmonary hypertension, cardiovascular diseases, carcinogenic disorders and many inflammatory diseases [7-11]. One of such inflammatory bowel disease is ulcerative colitis which affects the part of colon and rectum [12]. Inflammation forms ulcer on the lining of the colon which causes rapid movement of bowel [13]. Symptoms of UC are Abdominal pain, bloody diarrhoea, fatigue, pale skin, poor appetite and weight loss, loss of bowel movement control, slow growth and development in children [14,15]. These symptoms are due to mucosal layer loss which was covering large intestine inner wall [16].

In recent studies it is observed that Western and European countries are persisting UC up to 90-505 per 100,000 [2,17]. Comparatively, Japan has low prevalence of UC [18,19].

The shielding effect of smoking is for a time being since the relative peril for the disease aggravate after the termination of smoking, as compared to non-smokers [20,21]. It is being observed that smoking cigarette causes increase in the disease activity. It is said that smoking cures the disease, is due to presence of nicotine. Nicotine is active moiety of cigarettes which is used for medicinal purposes in the case of ulcerative colitis and is also dispensed in the form of chewing gum, transdermal patches, and nicotine-based enemas [22-24]. Direct use of nicotine is more effective as compared to smoking but should be used in a limited quantity [25-28]. Although there are few Food and Drug Administration, USA (FDA) approved drugs for the treatment of IBD's like certolizumab pegol, golimumab, mesalamine, budesonide, etc. Corticosteroids, antitumor necrosis factor and immune-suppressants are widely known for IBD treatment [29]. Recently herbs are used for the treatment of IBD [30-34]. If ulcerative colitis is not treated, it can cause malnutrition, dehydration, and anemia leading to increased risk for colorectal cancer [35,36]. Recent study suggests that nicotine is incurable for the active colitis [26].

Pouch contraction in a patient decides whether it is in initial stage or at last stage. In early stages Small-Bowel Obstruction (SBO), portomesenteric vein thrombosis, and pelvic sepsis takes place with the leak of J-pouch tip or body. In later stages aggravated symptoms are observed which are classified as twisted pouch, adhesive SBO, pouch prolapse, limb syndrome, afferent and S-pouch efferent limb syndrome, inflammation, fistulas, anovaginal and pouch-vaginal fistulas among female patients.

Out of 100, 30% patients with UC require surgery [37,38]. Pouchoscopy is used for the treatment of neoplastic complications and inflammatory pouch in UC patients. Ileal Pouch Anal Anastomosis (IPAA) creates a neorectum and connects it with a sphincter to maintain continence. Although this operation satisfies high rate of patients but some experience poor quality of life continued with decrease in emotional or social quality of life [39,40].

UC Developing Peril

In many studies it is shown that UC affects non-smokers and former smokers, and protective effect is exerted by smoking in UC [41]. For more than 30 year relationship is found between UC and smoking. Samuelsson [41], observed medicine interaction rather than pathogenesis.

Harries et al. [42] in 1982, found in a study that out of 23 UC patients, 8% were current smokers. In meta-analysis 2.9 (95% CI: 2.6-3.2) ratio of non-smokers were at the risk of acquiring UC [20]. Also, it was demonstrated that former smokers were at high risk for acquiring the disease as compared to non-smokers in the ratio of 1.64 (95% CI: 1.36-1.98). It was found that increase in smoking caused decrease in disease risk. A meta-analysis [43] indicated with new information where 11, 741 patients with UC were confirmed with previous data. In contrast to smoking individual with never smoking individual, UC was found depleted in smoking individual with (OR: 0.58, 95% CI: 0.45-0.75), indicating a protective effect of smoking hence, suggesting individual who smoke show 42% depleted risk of UC diagnosis. Smoking among UC patients when compared with non-smoking UC individuals, showed an aggravate risk of UC with 1.79 (95% CI: 1.37-2.34) [44].

In studies of family smoking influenced genetically predisposed patients with IBD. There is relationship between smoking habits and phenotype of IBD, with non-smokers developing UC and smokers with CD [45]. Smoking protective effect on UC may be due to medicinal effect of tobacco but in some cases CD develops rather than UC as a result of smoking influence on the process of pathogenesis [46].

Dominant IBD and smoking 89 pairs of siblings suffering from CD or UC were investigated whether they showed similarity in genetic susceptibility for the IBD type or not [47]. Out of 89 pairs of siblings 21 suffered from CD those were smoking while non-smokers suffered from UC this study suggested that consumption of tobacco can act on genetic predisposition of IBD by shifting the phenotype from UC to CD.

On twins role of smoking was studied where 103 pairs were examined in which it was found, lower frequency rate of smokers among twins with UC [48]. For dissimilarity of disease smoking was found to be significant [49].

Influence of gender smoking on UC is again a topic of issue. In a study by Motley et al. [50] showed delay in disease onset in men but not in women. Bridger et al. [47], studied about how smoking may influence on females and males in correlation with CD and UC. This study revealed protective effect from UC (OR 0.18, 95% CI: 0.11-0.3) in smoking females rather than non- smoking females (OR 0.47, 95% CI: 0.28-0.79). Later in a study by Cosnes et al. [51] it was observed that significant effect of smoking in UC modulated by gender that showed cessation of smoking will cause aggravated risk of disease in men [52].

In a meta-analysis it was analysed that there is no chance for the development of UC in children who are passively exposed to smoking [53]. This analysis in actual is failure it is possible to develop UC on the exposure of smoking until it reach to its threshold level. Heide et al. [54] observed patients who smoke passively show higher risk to develop illeal diseases (pouchitis and backwash ileitis) as compared to UC patients who smoke non-passively.

Although data presented supports the protective effect of smoking in case of UC yet it is not concluded that smoking plays crucial role in treatment of UC.

Smoking Influence on UC

Ulcerative colitis is protective to smokers instead of non-smokers [55,56]. The rate of colectomy is lower in smokers as compared to non-smokers. There is decrease in colectomy risk of UC patients from 0.42 to 0.32 by smoking.

Beaugerie et al. [57], studied the cessation impact of smoking on UC, they observed no difference in rate of colectomy of patients who ceased smoking after diagnosis either were non- smokers or were chain smokers. Moreover, patients who quit smoking showed increment in the activity of the disease.

Beaugerie et al. [57], Boyko et al. [58] observed by the onset of UC the patients who were smoking were hospitalized less, while rate of colectomy was not identified in case of smokers and non-smokers.

Ex-smokers who were back to smoking showed improvement in symptoms also patients noted symptom of exacerbation when they quit smoking [27,59], they were relieved when smoked again [50].

Smoking shows protective factor in terms of proximal extension. Smoking patients showed less unprogressive extension of disease in terms of distal UC as compared to non-smoking patients [27]. France analysis showed rate of pancolitis lower in smokers instead of non-smokers [28]. Recently, Meucci et al. [60] described that non-smokers had higher rate of proximal extension.

Pica et al. [61] evaluated ulcerative proctitis in 138 patients in which 30% of patients showed proximal extension of the disease.

Many studies failed to reveal the importance of smoking in the case of UC [62-64]. In a survey Roth et al. [24] admitted 102 patients to assess disease history and predicted severity of future disease at diagnosis time. Gender, family history of IBD, smoking status and disease severity did not predict severity of the disease. Romberg-Camps et al. [65] studied recurrence rates as for the use of cumulative medicines, severity of disease and surgical and nonsurgical as the outcome parameters. This study creates the doubt about protective effect of smoking on disease recurrence in UC.

Action of mechanism of nicotine and smoking is unknown in case of UC [66]. Usually it is said that nicotine plays key role in UC patients however there is no proof regarding this. Nicotine in UC patients causes increase in synthesis of mucin [67]. UC patients have thin mucus layer of rectum and colon as compared to healthy people [68].

Immune system is affected by nicotine. It may be possible that heavy smokers may lack immunoglobulin A in their intestinal secretion and saliva [69,70]. Cellular immune-defense mechanisms is influenced by heavy smoking which may lead to immune suppression with an aggravate level of CD8+ T cells suppressor [71,72]. Pro-inflammatory molecule synthesis is decreased by nicotine [73].

UC smokers have a mucosal cytokine levels reduction, mostly IL-1b and IL-8 [74,75]. A serviceable nicotine effect in active UC is associated with a decrease in IL-8 expression [76]. It was found that in passive smoking rats there was improvement in DNBS-induced colonic damage involving cytokine colonic level changes. Leukotriene B4, TNF-α, IL-1β, and IL-6 level when increased caused problem [77]. In disparity, during UC deprivation of IL-10 was preserved. In cytokine balance these changes are still unknown [78,79].

Phagocytic function, bactericidal and bacteriostatic activity is depleted due to smoking. Those rats which were exposed to nicotine showed inhibition response of antibody cell formation continuously by impairing antigen mediated signalling in T-cells and induced T-cell energy [80].

Smoking generates free oxygen radicals with depleted capacity of antioxidants [81]. This fact shows the hazardous effect of smoking on CD patients also show no beneficiary effects on UC patients.

Rectum's hypoperfusion and colonic tissue damage, alteration of gut motility, the reduction of smooth muscle tone and contractility [82], altered permeability [83], and alterations in the microcirculation [84] are some other harmful effects of nicotine or smoking [85]. Intestinal permeability is increased of the IBD patients [86]. In healthy people it was found decrease in the intestinal permeability [87]. Therefore, no such observations can be compared with UC smokers and non-smoking patients of UC [88] by proving the notion wrong that UC is cured by smoking.

Nicotine: Mechanism of Action

It is difficult to track out the mechanism indulged in the medicinal effect of nicotine in the condition of UC. Thickness of colonic mucus is increased by nicotine hence, protecting the intestinal mucosa [89], as reported in many studies. It is described [65] that nicotine causes blood flow reduction in intestine, unlikely this may account favourable effects of smoking. In colon secretion of mucine is increased which causes release of NO and have properties of anti-inflammation [90] Rectal supply of blood in UC condition is low as compared to healthy person [91].

In chronic inflammatory diseases like IBD's animal models were used which reveals involvement in cytokine pathway [92]. Cellular and the humoral immune system were found to be influenced by nicotine [93] as a response [94]. Production of interleukin-10 is inhibited by Th2 cell *in vivo* with the help of nicotine [95], and additionally mononuclear cells reduce production of interleukin-2 [96] and interleukin-8 [97].

Prytz et al. [87] reported the tightening of gut in healthy person and demonstrated that smokers have low intestinal permeability that might explain for protective effect of smoking in ulcerative colitis. Suenaert et al. [83] found the reducing effect of NSAIDs on permeability of intestine through smoking. It was also observed that there was no smoking effect on the permeability of small intestine of a healthy person. Benoni et al. [88] observed that permeability of intestine has no difference whether a person is smoker or not. These studies were contradictory about the complexity of the impact of UC on permeability of intestine in conjunction with smoking.

Beneficial effects of nicotine in case of Ulcerative Colitis are yet to be determined; its adverse effects cannot be denied [98].

Termination of Smoking

UC dealing patients who cease smoking suddenly can potentially face increase in its symptom can also decrease the activity of the disease. This reason makes a UC patient decide whether he should quit smoking or not [98].

It is important for a patient to be aware of the active cigarette smoking which causes many diseases such as vascular disease, cancer, coronary heart disease, lung cancer, respiratory symptoms and chronic obstructive pulmonary disease.

It is important to give information to the patient about exacerbation of disease such as flares, hospitalization or the need for oral steroids by smoking cessation [99]. Not only this, it is important for patient to know about the risk of colectomy which should not be aggravated by quitting smoking.

Pulmonary cancer risk is decreased in case of UC patients [100]. Smoking increase the risk of colon cancer should be informed to the UC patients. A recent studied showed about the increasing risk of colon cancer to the smokers (CRC) [101].

There are many treatments to control inflammation after cessation of smoking eg. leukocyte apheresis, immunosuppressant or anti-TNF-α products [102].

These hazardous effects with substantial prevalence, represents smoking as a wider cause of death worldwide. Hence, there is no such protective effect by smoking, so doctors should advice patients with UC to quit smoking.

Conclusion

Although smoking provides protective effect to Ulcerative colitis but it causes several other health issues and diseases. Avoiding smoking is preferably better as the most important role in treating Ulcerative colitis is of nicotine. As Nicotine is active moiety of cigarettes which is used for medicinal purposes in the case of ulcerative colitis and is dispensed in the form of chewing gum, transdermal patches, and nicotine-based enemas. Consumption of nicotine can be used to treat Ulcerative colitis but in limited quantity as it is always said excess of anything is hazardous.

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