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Is smoking a risk factor for collagenous colitis?

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Swedish Organisation for study of Inflammatory Bowel Disease (SOIBD)

Short title Smoking in collagenous colitis

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Abstract

Objective. The association between smoking and idiopathic inflammatory bowel disease is well known; smoking seems to have a diverse effect. Crohn´s disease is associated with smoking, while ulcerative colitis is associated with non-smoking. Data on smoking in microscopic colitis of the collagenous type (CC) is lacking. The aim of this investigation was to study smoking habits in collagenous colitis and to observe whether smoking had any impact on the course of the disease. **Materials and Methods.** 116 patients (92 women) with median age of 62 years (IQR 55-73) answered questionnaires covering demographic data, smoking habits and disease activity. As control group we used data from the general population in Sweden retrieved from the National Statistics Office of Sweden, the central bureau for national socioeconomic information. **Results.** Of the 116 CC patients, 37% were smokers compared to 17 % of controls ($p<0.001$, OR 2.95). In the age group 16-44 years, 75 % of CC patients were smokers compared to 15 % of controls ($p<0.001$, OR 16.54). All CC smoker patients started smoking before the onset of disease. Furthermore, smokers developed the disease earlier than non-smokers – at 42 years of age (median) compared with 56 years in non-smokers ($p<0.003$). Although the proportion with active disease did not differ between smokers and non-smokers, there was a trend indicating that more smokers received active treatment (42% vs. 17%), $p=0.078$). **Conclusions.** Smoking is a risk factor for collagenous colitis. Smokers develop their disease more than ten years earlier than non-smokers.

Key words: Collagenous colitis, Crohn´s disease, microscopic colitis, smoking, ulcerative colitis.

Introduction

Crohn´s disease (CD) and ulcerative colitis (UC) are immune-mediated diseases, caused by an interaction of genetic and environmental factors, resulting in a chronic, macroscopic intestinal inflammation. In contrast, collagenous colitis (CC) is characterised by a macroscopically normal or nearly normal colonic mucosa but with distinctive histopathological features, including chronic inflammation in the lamina propria, a thickening of the subepithelial collagen layer and epithelial cell damage with or without an increased number of intraepithelial lymphocytes. The condition was first described in Sweden in 1976 [1] and is characterized clinically by chronic watery diarrhoea and has a female predominance with a peak incidence in 60-year-old individuals. [2]

Drugs, luminal factors and infections are factors discussed in the development of CC, but the aetiology is still unknown. [3-5]. Familial occurrence has been reported indicating a possible genetic predisposition [6-8]. Furthermore, concomitant autoimmune diseases are prevalent so immunogenetic factors may influence the risk.

In UC and CD smoking seems to have important but diverse effects. Smoking has aggravating effects in CD but seems protective in UC. In CC only a few studies report smoking habits, and the role of smoking in CC is therefore still unknown. In 1999, Baert et al presented data on smoking habits in patients with microscopic colitis. Of 96 CC patients, 25 % were smokers and 8% ex-smokers. In contrast , 14% of 80 patients with lymphocytic colitis (LC) were smokers and 23% ex-smokers[9]. In another study by Chan [10] an increase in the relative risk of lung cancer was noted in women with

CC, which may also support the hypothesis that CC patients smoke more than the background population. In a study of 81 LC patients from 2004, 47% were smokers, 31 % were ex-smokers and 22 % had never smoked.[11] In an abstract presented in 2009, smoking was frequent in both CC (115 patients) and LC (97 patients) with OR 1.8 in CC and 2.1 in LC patients respectively. [12] In a small study by de la Iglesia 7 out of 18 patients were smokers [13] .

The aim of this study was to address the relationship between collagenous colitis and smoking, and to determine whether smoking habits have any impact on the clinical course of the disease.

Methods

Patients

In Sweden, patients with CC are usually seen at specialist gastroenterology units. This study was conducted among members of the Swedish Organization for the study of Inflammatory Bowel Disease (SOIBD). Eligible subjects were identified from patient registers at the university hospitals in Linköping, Örebro, Malmö and Gothenburg.

The diagnosis of CC was based on clinical symptoms and characteristic histopathological findings in the colon, showing a thickened subepithelial collagen layer ≥10 μm, a chronic inflammation in the lamina propria and flattening, vacuolisation or detachment of the surface epithelial cells with intra-epithelial lymphocyte infiltration. [14]

Questionnaires

In 2003, in order to evaluate the health-related quality of life of CC patients, 180 individuals received four health-related quality of life (HRQOL) questionnaires, a symptom diary and an additional questionnaire about present and past smoking habits. Data on the population studied and HRQOL results have been presented earlier [15].

Controls

Smoking data for the Swedish background population 2003 were retrieved from Statistics Sweden, the central bureau for national socioeconomic information. That year 6192 individuals were interviewed about their smoking habits and could be used as a control group. Statistics Sweden is an administrative agency whose main task is to collect statistics for policymaking, debate and research. In addition to producing and communicating statistical data, Statistics Sweden support and coordinate the Swedish system for official statistics as well as participate in international statistical surveys. This organisation is assigned by the government to register statistical information on socio-economic factors such as living conditions, health, smoking habits etc in society, something that has been done every year since 1975.

Statistics

Data is presented as median and inter-quartile range (25^{th} – 75^{th} percentiles). Group comparisons between smokers and non-smokers have been carried out with Chi2 and were used to calculate odds ratio (OR) with corresponding 95% confidence intervals (CI). Differences in age at disease onset between smokers, ex-smokers and non-smokers were calculated using Mann-Whitney and Kruskal-Wallis tests. Differences in disease

activity between smokers and non-smokers were estimated with Chi2-test. A P-value <0.05 was considered significant.

Ethics

The local Committee of Research Ethics at each hospital approved the investigation and the participants gave written informed consent before participating.

Results

Patients

Of 180 patients, 116 patients (64%) completed the questionnaire. There were 92 (79%) women and 24 (21%) men with a median age of 62 (IQR 55-73) and disease duration of 8 (IQR 5-17) years. Respondents did not differ significantly from the whole study population (180 patients), in which 84% were women with a median age of 64 (IQR 57-74) years.

Smoking data

As described in Figure 1 and Table I, smoking was more prevalent in CC patients compared with controls. The frequencies of smokers were 37% among all CC patients and 17% in the control group (totally 6192 individuals) ($p<0.001$, OR 2.95). 75% of CC patients in the age group 16-44 years (9 out of 12) were smokers compared to 15% in the control group (2573 individuals) ($p<0.001$, OR 16.54). The difference in smoking between CC patients and the control group decreased with increasing age. Based on Chi-2 analysis all age groups (except those aged 65 and above) as well as the total

group differed significantly from the control group. The confidence intervals for the odds ratio exceeded 1 for the total group but also for all age groups except the oldest one. In Table I the OR and 95% CI for the different groups are stated. Because of the rather small cohorts OR has only been calculated for the whole groups and not for men and women separately except in the age group 16-44 where the group of smoking CC patients only consisted of women.

Clinical symptoms including number of bowel movements, abdominal pain and number of loose stools /day during one week were registered by 107 of 116 patients. If a patient had more than three bowel movements per day or daily diarrhoea, criteria for active disease, as defined earlier, were fulfilled [16]. Of these 107, 45 patients had active disease at the time of the interview (9 were treated with budesonide) and 62 had inactive disease (13 treated with budesonide). As can be seen in Figure 2 smoking habits did not affect disease activity (p=0.27) although there was less activity among those who had never smoked. Despite the fact that 47% of smokers had active disease as compared to 34% of "never smokers", this did not reach statistical significance (p=0.27). In accordance with this observation, there was no correlation between frequency of abdominal pain and active smoking (data not shown). Among the patients with inactive disease (N=62) 23 were non-smokers, 20 were ex-smokers and 19 were active smokers. Of the 23 non-smokers, 4 received budesonide treatment (17%) compared to 8 of the 19 smokers (42%, p=0.078 with Chi2-test).

Twenty six non-smoking patients, 24 ex-smokers and 33 current smokers could state their age when they first noted symptoms from the disease. The median age of these were 56 (45-70), 54 (43-63) and 42 (30-57) years respectively. The difference between

smokers and non-smokers was significant in the Mann-Whitney test (p=0.003) as well as the difference between all three age groups when applying the Kruskal-Wallis test (p=0.005). Smoking patients with CC had started smoking 17 (median) (8-31) years before the onset of the disease. All of them started to smoke before they were diagnosed with CC. The interval from onset of symptoms to diagnosis was two (median) (1-9) years.

The patients had about the same educational level as the average for society as a whole. 113 of 116 patients answered questions about their level of education. 61/113 (54%) had up to 11 years of school, i.e. upper secondary school, compared with 58% in the control group of the same age.

The mean body mass index (BMI) was 24.1 for women (range 16-37.6, data available for 90 persons) and 25.3 for men (range 21.5-29.2, data available for 23 persons) compared to 24.4 and 25.5 respectively in the control group (estimated in the age group 16-84 years).

Discussion

In the present study we found data supporting a correlation between CC and smoking. A high occurrence of smokers in our studied cohort was found, approximately twice as high as in the background population. Even if the number of patients in this study is low, the difference can be observed in all age groups. Especially in the younger age groups the difference is pronounced and can be appreciated both with analysis based on

Chi2 and OR. The deviation is slightest, and not significant, among the oldest patients (above 64 years of age). An association between CC and smoking is further supported by Chan et al who found a significantly increased relative risk of lung cancer in women with CC, a condition strongly correlated with smoking [10]

The link between smoking and IBD was first made by Harries et al [17] when they noted that only a low proportion of UC patients were smokers. Later Somerville et al [18] reported a higher relative risk in smokers of developing CD. In patients with CD, 45-55% smoked as compared to a control group matched for age and gender where 30-40% smoked [19]. An important question is why this association exists. Even though CC differs from CD in many ways, i.e. localisation, severity, course of disease, both conditions show a correlation with smoking. Smoking increases the risk for CD and also implies a more complicated disease pattern. By contrast, there is an increased risk for relapse in patients with UC that stop smoking[20]. The mechanism for this is not clear and many hypotheses have been suggested. It has been shown that smoking affects the immune system – both cellular and humoral immunity are affected [21]. Macrophages in smokers have a deficiency in their ability to kill intracellular bacteria [22]. Nicotine has immunosuppressive effects and decreases the synthesis of IL-1 and TNF, central players in the immune response [21]. In ulcerative colitis the colonic mucus layer is thin, in contrast to Crohn´s disease where the layer is thicker [23]. In CC there is a thickened layer of collagen and the question is whether these effects in the mucosa in CC and Crohn´s disease are both results of defence mechanisms in the gut epithelium. Furthermore, smoking tends to increase the thrombotic potential and leads to changes in microcirculation which can also cause ischemic changes to contribute to how the illness

develops [24]. In addition, smoking is responsible for a reduction of smooth muscle tone and contractility as well as decreased permeability[20].

Baert et al reported in 1999 that 25% of their CC patients smoked as compared to 14% of the patients with LC. In CC 8% were ex-smokers compared to 23% in LC [9]. The question is whether the different types of microscopic colitis (as well as other inflammatory bowel diseases) could share the same genetic predisposition, while smoking or other environmental factors could influence the development towards either CC or LC. Another possibility is that smoking could lead to a more severe disease with a deeper inflammation and as a consequence fistulas and strictures in Crohn´s disease and – in line with that – development of a possible protective collagen layer that is diagnostic in CC.

In a case report describing the illness in two sisters, one had CC and was a smoker while her sister had LC and did not smoke [7]. Similar observations have been made in IBD where siblings that were smokers tended to develop CD while non-smokers developed UC.
[25, 26] In CD, women are more affected by smoking and they have a higher relative risk, sometimes as much as three-fold [27].

Another controversy to consider is whether CC really is associated with smoking or alternatively if this subtype of colitis and smoking both share some common background factor that is not yet identified. If for example a certain kind of personality trait with more sensitivity to stress is correlated both with an increased tendency to

smoke and to a certain kind of immune activation in the gut, the observed relationship is not causal but instead coincidental.

Even though the response rate (64%) is fair it would have been better if we had succeeded in getting a rate at least exceeding 70%. Since smokers seem to have CC to a higher extent than the control group a selection bias cannot be excluded. Unfortunately, quite some time has elapsed why it may be difficult for those included afterwards to remember and answer in an appropriate way. Despite this weakness the previously observed association with lung cancer (ref Chan) and the differences in smoking habits between CC and LC found by Baert (ref) indicates that the observed association with smoking could be in accordance with reality.

In our patients the disease activity seemed to be influenced by active smoking although the difference between smokers and non-smokers did not achieve statistically significance. We did not have access to information on amounts of tobacco consumption and thus could not address the question whether there was a correlation between degree of tobacco use and disease activity

Since inactive disease could be a consequence of more active treatment with budesonide, the main drug of choice for treatment of CC in Sweden, we compared the number of treated patients with inactive disease among smokers with that in non-smokers. There was a trend indicating that more smokers than non-smokers received active treatment (42% compared to 17%, p=0.078). Consequently, although we cannot confirm the association between smoking and disease activity, it could be hypothesised that smokers may have a higher rate of active disease than non-smokers. Further studies

including a larger number of participants are needed to investigate this matter. In order to be able to evaluate this aim we have compared the disease activity in smoking CC patients to non-smoking CC patients. Due to the design of the questionnaire it is unfortunately not possible to retrieve information on bowel habits in the control group.

Since smokers showed signs of disease at a much lower age than non-smokers and ex-smokers, it seems as if smoking could initiate a latent disease that otherwise might develop much later in life. The difference in age at diagnosis between smokers and those who had never smoked was as much as 14 years. This difference has not been observed in CD patients where the age at onset was similar for smokers and non-smokers (28.3 years and 28.9 years) [28].

The educational level in CC patients did not differ in any substantial way from that of the background population. Even if we did not study this putative correlation in detail in this investigation, the observation raises the question whether there could be a difference from the conditions in IBD where a high educational level predisposes for IBD, in line with the hygiene hypothesis[29].

In conclusion, this multicenter study of smoking habits in patients with CC has established an association between collagenous colitis and smoking. The finding that smoking is common in patients with CC is in line with previous findings of increased frequency of lung cancer in these patients. Smoking has many biological effects but one can only speculate on the possible link in this respect between CC and CD, another inflammatory bowel disease linked to smoking.

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Figures and Tables

Figure 1

Daily smokers in the control group compared with smokers among patients with collagenous colitis

Figure 2

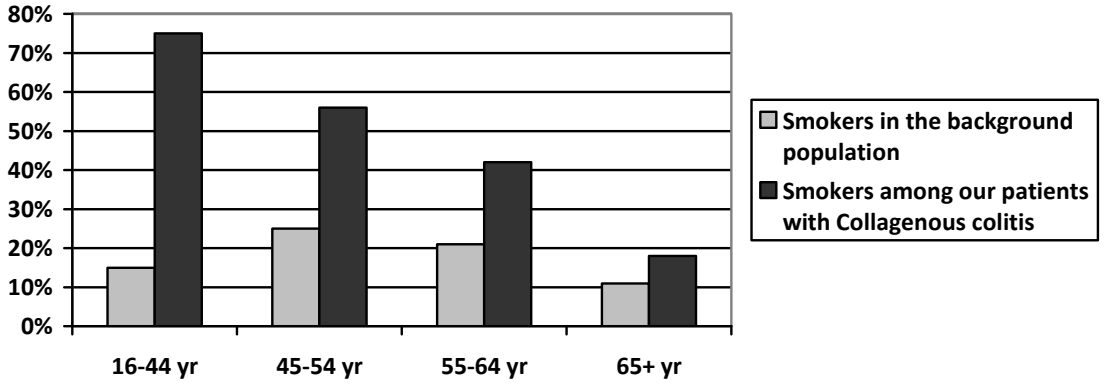
Disease activity in patients with collagenous colitis in relation to smoking habits

Table I

Daily smokers in the control group compared with smokers among patients with collagenous colitis

Figure 1

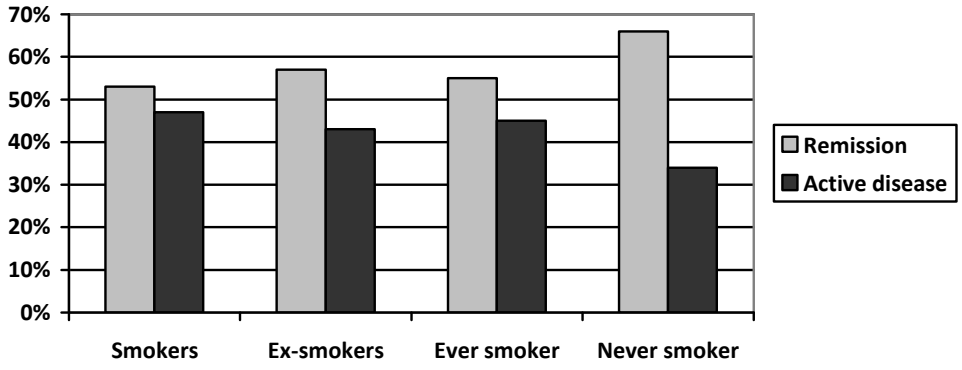
Daily smokers in the control group compared with smokers among patients with collagenous colitis



P-values: 16-44 years < 0.001; 45-54 = 0.0048; 55-64 = 0.0020; 65+ = 0.12

Figure 2

Disease activity in patients with collagenous colitis in relation to smoking habits



Ever smoked = current smokers and ex-smokers

Table I

Smokers in control group

Age (years)	Total (%)	Women (%)	Men (%)
16-44	395/2573 (15)	223/1282 (17)	172/1291 (13)
45-54	249/989 (25)	130/518 (25)	119/471 (25)
55-64	205/977 (21)	109/490 (22)	96/487 (20)
65+	182/1653 (11)	89/907 (10)	93/746 (12)

Smokers among patients with Collagenous colitis

Age (years)	Total (%)	Women (%)	Men (%)
16-44	9/12 (75)	9/12 (75)	0 (0)
45-54	9/16 (56)	6/12 (50)	3/4 (75)
55-64	16/38 (42)	14/32 (44)	2/6 (33)
65+	8/49 (16)	5/36 (14)	3/13 (23)

Comparisons between smokers in the control group and patients with collagenous colitis

Age (years)	Control group (%)	Colitis (%)	OR (CI)
All age groups	1031/6192 (17)	43/116 (37)	2.95 (2.01;4.32)
16-44 (all)	395/2573 (15)	9/12 (75)	16.54 (4.46;61.37)
16-44 (women)	223/1059 (21)	9/12 (75)	14.25 (3.83;53.05)
45-54	249/989 (25)	9/16 (56)	3.82 (1.41;10.37)
55-64	205/977 (21)	16/38 (42)	2.74 (1.41;5.31)
65+	182/1653 (11)	9/50 (18)	1.77 (0.85;3.71)

Daily smokers in the control group compared with smokers among patients with collagenous colitis

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