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Increasing incidence of microscopic colitis in a population-based cohort study in Switzerland

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Increasing incidence of microscopic colitis in a population-based cohort study in Switzerland

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préparée sous la direction du Professeur Alain SCHOEPFER

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Hugo MAYE

Médecin diplômé de la Confédération Suisse
Originaire de Chamoson (Valais)

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Increasing incidence of microscopic colitis in a population-based cohort study in Switzerlandg

Lausanne, le 11 février 2021

pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Résumé en français

Contexte: Les colites microscopiques (CM) sont des pathologies faisant partie des maladies inflammatoires de l'intestin et se traduisant principalement par des symptômes digestifs tels que diarrhées et douleurs abdominales, mais à la différence de la maladie de Crohn et de la colite ulcéreuse, elles sont caractérisées par un aspect macroscopique normal. Le diagnostic repose donc sur la base de biopsies prélevées lors de colonoscopies démontrant des critères histo-pathologiques stricts. Les données épidémiologiques concernant la fréquence et l'histoire naturelle des CM sont rares. Notre étude a eu pour but d'évaluer la présentation clinique des CM au moment du diagnostic, l'incidence et la prévalence ainsi que l'histoire naturelle et sous traitement des CM dans les cantons de Vaud et Fribourg en Suisse.

Méthode: En 12.2017, le nombre d'habitants dans les cantons de Vaud et Fribourg était de 1'109'230. Après avoir identifié les patients diagnostiqués avec une CM à travers les bases de données des différents instituts de pathologie de ces cantons (n=6), nous avons créé une base de données applicable à l'ensemble des patients et avons effectué une récolte de données auprès des différents gastro-entérologues installés et hospitaliers.

Résultats: Nous avons inclus un total de 218 patients diagnostiqués avec une CM. Parmi ces patients 123 présentaient une colite microscopique lymphocytaire (CML) et 95 une colite microscopique à collagène (CMC). L'incidence des CM a augmenté de façon significative de 0.36/100'000 habitants durant la période 1994-1997 à 6.85/100'000 habitants en 2017 (p=0.025). La prévalence cumulée des CM, CML et CMC en 2017 était respectivement de 19.65/100'000, 11.09/100'000 et 8.56/100'000. La durée médiane de suivi clinique était de 4 ans (IQR 2-7, intervalle 0-22 ans). 62% des patients présentaient une forme légère (< 1 poussée/an), 28% présentaient une forme modérée (au-moins 1 poussée/an), et 10% présentaient une forme chronique. L'arrêt du facteur favorisant (par ex: IPP, statines, SSRI, tabac) était significativement associé à une forme clinique légère (p=0.013) avec l'utilisation de modèles de régression logistique.

Conclusions: L'incidence et la prévalence cumulée des CM ont montré une augmentation marquée dans une région indicatrice spécifique de la Suisse. Environ 2/3 des patients étaient caractérisés par une forme clinique légère.

Increasing Incidence of Microscopic Colitis in a Population-Based Cohort Study in Switzerland

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Microscopic colitis (MC) is a chronic inflammatory disease of the colon that presents with chronic, nonbloody watery diarrhea and only few or no endoscopic abnormalities. Histologic examination discriminates lymphocytic colitis (LyC; presence of $\geq$20 intraepithelial lymphocytes per 100 surface epithelial cells) and collagenous colitis (CC; colonic subepithelial collagen band >10 μm in diameter).[1,2] MC not otherwise specified describes a subgroup of patients who do not fulfill the diagnostic criteria for either CC or LyC.[1,2] Population-based epidemiologic data regarding MC are scarce. We aimed to evaluate the clinical presentation at diagnosis, incidence, and prevalence of MC in Cantons of Vaud and Fribourg, Switzerland.

Methods

Cantons of Vaud and Fribourg lie in the French speaking, Western part of Switzerland. As of December 2017, both cantons together had a population of 1,109,230 inhabitants. After having identified patients with MC through databases of all pathology institutes (n = 6) serving both cantons and a histology slide review to ensure correctness of diagnosis, we performed a chart review in practices of all gastroenterologists covering both cantons (n = 42). The study was approved by the ethics committee of Cantons of Vaud and Fribourg (CER-VD 306/15). Two hundred and fifty-two patients with MC, diagnosed between January 1994 and December 2017, were identified. Of these, 34 were excluded for having MC not otherwise specified. We calculated incidence rates using data provided by the Institutes of Population Statistics of Canton of Vaud and Fribourg.

Results

Of the 218 patients with MC, 123 (56.4%) had LyC and 95 (43.6%) had CC. Seventy-four percent (162/218) of patients with MC were female, mean age at first symptoms was 62 $\pm$ 15.4 years (range, 24–89), and mean age at MC diagnosis was 63.2 $\pm$ 14.3 years (range, 29–89). All patients with MC suffered from diarrhea, followed by abdominal pain (31.7%), weight loss (31.2%), bloating (20.6%), fatigue (9.6%), and nausea/vomiting (3.2%). Exposure to risk factors for MC were frequently found and included HMG-CoA reductase inhibitors (27.1%), nonsteroidal anti-inflammatory drugs (14.2%), proton pump inhibitors (22.5%), serotonin reuptake inhibitors (22.5%), and smoking (20.2%). Infectious agents were searched and excluded as cause of chronic diarrhea in all included patients.

A colonoscopy was performed as diagnostic tool in all 218 patients. In 74.3% of patients the colonoscopy was normal. Polyps were found in 16.5% of patients with MC, followed by edema (9.2%), erythema (4.6%), and an erosion (0.5%). Median thickness of the subepithelial collagen band in patients with CC was 25 μm, whereas patients with LyC had a median of 35 intraepithelial lymphocytes per 100 epithelial cells.

Oral budesonide was most frequently used as first therapy (72.9%), followed by loperamide (66.1%), aminosalicylates (16.1%), and cholestyramine (12.8%).

Incidence rates were calculated and are shown together with the cumulative prevalence in Table 1. No patient was diagnosed with MC before 1994. Incidence of MC significantly increased from 0.36/100,000 person-years in 1994–1997 to 6.85/100,000 person-years in 2017 ($P = .025$, trend test). The cumulative prevalence of MC, LyC, and CC in 2017 was 19.65/100,000, 11.09/100,000, and 8.56/100,000, respectively. As such, the current prevalences for MC, LyC, and CC are 1/5088 persons, 1/9018 persons, and 1/11,676 persons, respectively.

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Table 1. Incidence (Plus 95% Confidence Intervals) and Prevalence of MC, LyC, and CC From 1994 to 2017

Interval	1994–1997	1998–2001	2002–2005	2006–2009	2010–2013	2014–2017
Population Vaud + Fribourg	839,965	856,091	901,168	967,802	1,027,985	1,109,230
MC new cases	3	8	22	45	64	76
MC incidence per 4-y interval	0.36 (0–0.48)	0.93 (0.48–1.4)	2.44 (2.2–2.68)	4.7 (3.32–5.8)	6.23 (5.44–7)	6.85 (6.12–7.56)
MC incidence per year	0.09	0.23	0.61	1.18	1.56	1.71
MC prevalence	0.36	1.29	3.66	8.06	13.81	19.65
LyC new cases	1	5	16	27	35	39
LyC incidence per 4-y interval	0.12 (0–0.48)	0.58 (0.48–0.92)	1.78 (1.32–2.2)	2.79 (2.48–3.32)	3.41 (2.72–3.88)	3.52 (2.88–3.96)
LyC incidence per year	0.03	1.5	0.45	0.7	0.85	0.88
LyC prevalence	0.12	0.7	2.44	5.06	8.17	11.09
CC new cases	2	3	6	18	29	37
CC incidence per 4-y interval	0.24 (0–0.48)	0.35 (0–0.48)	0.67 (0.48–0.89)	1.86 (1.24–2.48)	2.92 (2.72–3.12)	3.34 (2.88–3.6)
CC incidence per year	0.06	0.09	0.17	0.47	0.73	0.84
CC prevalence	0.24	0.58	1.22	2.99	5.64	8.56

CC, collagenous colitis; LyC, lymphocytic colitis; MC, microscopic colitis.
The incidence is shown per 100,000 inhabitants, stratified according to 4-year intervals and per year. The prevalence was calculated per 100,000 inhabitants at the end of the respective 4-year interval.

Discussion

Our population-based study from Western Switzerland found a steady increase in incidence of MC during the last 2 decades. Findings of our study are in accordance with the results of a systematic review and meta-analysis that reported pooled incidence rates for CC of 4.14 (95% confidence interval, 2.89–5.40) per 100,000 person-years and 4.85 (95% confidence interval, 3.45–6.25) for LyC. Bergman et al[3] assessed the incidence of MC in Sweden from 1995 to 2015 in a nationwide cohort. Among 13,844 patients, incidence of MC was 10.5/100,000 as from 2006, which is roughly 6 times higher when compared with our findings.[3] Our data are comparable with the results of Fernandez-Banares et al[4] who found lower incidences (2.2/100,000 for LyC and 2.6/100,000 for CC) among 290,000 inhabitants in Spain. These results reinforce the existence of a north-south gradient of MC which has been described by several groups.[5]

Strengths of our study are that all gastroenterologists and pathologists working in Cantons of Vaud and Fribourg collaborated in this project, which is crucial for the generation of population-based data. Limitations of our study are related to its retrospective design, which impairs the generation of high-quality data to evaluate questions regarding the natural history of MC, such as therapeutic response to different drugs.

In conclusion, in the first Swiss population-based study we found that MC incidence was steadily increasing over the last 2 decades. Compared with other countries, MC incidences are low in the population we studied.

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Conflicts of interest
The authors disclose no conflicts.

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Increasing incidence of microscopic colitis in a population-based cohort study in Switzerland

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ABSTRACT

Background & aims: Population-based epidemiologic data regarding the frequency and natural history of microscopic colitis (MC) are scarce. We aimed to evaluate the clinical presentation at diagnosis, incidence and prevalence, and natural course of microscopic colitis in Cantons of Vaud and Fribourg, Switzerland.

Materials and methods: Cantons of Vaud and Fribourg lie in the French speaking, Western part of Switzerland. As of 12/2017, both cantons together had a population of 1,109,230 inhabitants. After having identified patients through databases of all Pathology institutes (n=6) serving both cantons, we performed a chart review in practices of gastroenterologists in charge.

Results: We included 218 patients with MC, whereof 123 had lymphocytic colitis (LyC) and 95 collagenous colitis (CC). Annual incidence of MC significantly increased from 0.09/100,000 inhabitants in 1994to 1.71/100,000 inhabitants in 2017 (p=0.025). The prevalence of MC, LyC, and CC in 2017 was 19.7/100,000, 11.1/100,000, and 8.6/100,000, respectively. Median duration of follow-up was 4 years (IQR 2-7, range 1-22 years). A total of 62% of patients had a mild disease (defined as less than one flare per 12 months), 28% had moderate disease activity (defined as at least one flare per 12 months), and 10% had chronic ongoing disease. Stopping the offending agent (eg. statins, PPI) was significantly associated with a mild disease course (OR 3.13, p=0.013) in logistic regression modeling.

Conclusions: The incidence and cumulative prevalence of MC shows a steady increase in Western part of Switzerland. Roughly two thirds of patients were characterized by a mild disease course.

249 words

Key words: microscopic colitis, collagenous colitis, lymphocytic colitis, epidemiology, incidence, prevalence, population-based

INTRODUCTION

Microscopic colitis is a chronic inflammatory disease of the colon that presents with chronic, non-bloody watery diarrhea and only few or no endoscopic abnormalities. Histologic examination discriminates two subtypes of microscopic colitis, lymphocytic colitis and collagenous colitis.[1] Collagenous colitis is characterized by a colonic subepithelial collagen band >10 micrometers in diameter whereas the diagnosis of lymphocytic colitis relies on the presence of ≥20 intraepithelial lymphocytes per 100 surface epithelial cells. The term incomplete microscopic colitis or microscopic colitis not otherwise specified (NOS) is used to describe a subgroup of patients with diarrhea, an increase in cellular infiltrate in the colonic lamina propria, and either an abnormal collagenous layer or an elevated number of intraepithelial lymphocytes who do not fulfill the diagnostic criteria for either collagenous and lymphocytic colitis.[1] As of yet it is unclear if NOS should be considered a separate subtype of microscopic colitis as these findings can be observed in various conditions such as in ischemic colitis or irritable bowel syndrome.[2] Microscopic colitis mostly affects middle-aged patients and has a female predominance.[1,3-5] It has been associated with several other conditions with an autoimmune background, such as type 1 diabetes, and autoimmune thyroiditis.[6-8] Rarely, concurrent microscopic colitis has been found in patients with inflammatory bowel disease, in particular in patients with ulcerative colitis.[9] The incidence of collagenous colitis and lymphocytic colitis ranges from 2.0-10.8 and 2.3 to 16 per 100,000 per

year, respectively.[10-16] First data on the description of microscopic colitis date back to the early years of 1990's. Some studies have found an increase of the incidence of microscopic colitis whereas others did not. Given the lack of local data, we performed a population-based study in order to evaluate the incidence and prevalence of microscopic colitis, its clinical presentation, and its natural history in two cantons in the Western part of Switzerland.

METHODS

Canton of Vaud: Population characteristics and health care system

Cantons of Vaud and Fribourg are situated in the Western part of Switzerland which has about 8 million inhabitants. As of December 2017, Canton of Vaud and Fribourg had 794,384 and 314,846 inhabitants, respectively. Canton of Vaud and Fribourg are both mixed urban-rural regions. In 2017 a total of 27.1% of the Swiss population >15 years of age were smokers (31% men, 23.3% women). Smoking was defined as daily consumption of at least one cigarette.

As of December 2017, the gastroenterology service in Canton of Vaud for adult patients was provided by 32 Swiss board-certified gastroenterologists. Of those, 9 were working in CHUV University hospital, and 23 were working in private practice. Most gastroenterologists working in private practice were also affiliated with primary or secondary referral centers. The gastroenterology service for pediatric patients was provided by two pediatric gastroenterologists at CHUV.

As of December 2017, the gastroenterology service in Canton of Fribourg for adult patients was provided by 7 Swiss board-certified gastroenterologists. All of

122 them were working in private practice and had affiliations with primary or
123 secondary referral centers. The gastroenterology service for pediatric patients
124 was provided by one board-certified pediatric gastroenterologist at hôpital
125 cantonal de Fribourg.
126 The histopathology service in Canton of Vaud and Fribourg was provided by
127 pathologists working at the Institute of Pathology of CHUV or one of the following
128 five private histopathology institutes: ArgotLab, Aurigen, Institut Pathologie
129 Romand, Promed and Unilabs.
130

131 **Patients**

132 The study was approved by the ethics committee of Cantons of Vaud and
133 Fribourg (CER-VD 306/15). All pathologists and gastroenterologists of Canton of
134 Vaud and Fribourg participated in this study. Two hundred and fifty-two patients
135 with microscopic colitis, diagnosed between January 1994 and December 2017,
136 were identified by searching the electronic databases of all pathology institutes
137 (**supplementary Figure 1**). Participating pathologists reviewed the slides to
138 ensure the correctness of diagnosis. Patients with microscopic colitis fulfilled the
139 following published diagnostic criteria: 1) patients with collagenous colitis had to
140 be diagnosed with a colonic subepithelial collagen band >10µm in diameter; 2)
141 patients with lymphocytic colitis had to have at least 20 intraepithelial
142 lymphocytes per 100 surface epithelial cells. Thirty-four patients did not fulfill
143 diagnostic criteria for either collagenous or microscopic colitis and where thereby
144 classified as having microscopic colitis not otherwise specified. After identification

of patients with microscopic colitis through pathology databases the researchers then visited all participating gastroenterologists for a chart review (HM and AM). Questions were discussed between HM, AM, the pathologist and gastroenterologist in charge until consensus was reached. In case of missing data in the chart patients were called to provide supplementary information.

For the evaluation of disease evolution we applied the following definitions: 1) mild disease, characterized by less than one flare per 12 months follow-up time; 2) moderate disease activity; characterized by at least one flare per 12 months follow-up; and 3) severe disease, which we characterized as chronic ongoing disease with permanent activity. A flare was defined as bowel frequency ≥4/day for at least 2 weeks. Trigger factors for microscopic colitis were assessed at diagnosis. Patients were followed by the gastroenterologist in charge with a first follow-up visit at a median of 2 (IQR 1-4) months after MC diagnosis. Further consultations were performed typically in one year intervals with the exception of flares that necessitated immediate consulting.

Statistical analysis

Data of microscopic colitis patients were entered into an excel sheet (Microsoft excel 2010; Microsoft Corporation, Redmond, WA, USA). Statistical analyses were performed using stata (version 13.1, College Station, Texas, USA). Results of normally distributed numerical data are presented as mean±standard deviation (SD) and range, whereas non normally distributed numerical data are presented as median, interquartile range and range. The Fisher's exact test (two-sided) or

the Chi squared test was used to explore associations of categorical data in two independent groups. The Wilcoxon rank sum test was used to explore associations of non normally distributed numerical data in two independent groups and the t-test was used for normally distributed numerical data. We calculated incidence rates using data provided by the Institutes of population statistics of Canton of Vaud and Fribourg. Incidences were calculated in intervals of 4 yours with the population number of the fourth year of the interval as reference. In addition, annual incidences per 100,000 of population are reported. Stepwise multiple logistic regression modeling was performed in order to evaluate potential factors (gender, diagnosis of microscopic colitis, stop of the "offending agent" within 6 months after diagnosis of microscopic colitis, and exposure time to "offending agent(s)") that might be associated with a benign disease course. In case several risk factors were present we only took into account patients who stopped all of them. In a first step, potential associated factors were tested separately. In a second step, all factors with a p-value <0.1 were entered together into the multivariate logistic regression model. A P-value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics of patients with microscopic colitis

A total of 218 pediatric and adult patients were diagnosed with microscopic colitis between January, 1994 and December, 2017. Of these, 123 (56.4%) had lymphocytic colitis and 95 (43.6%) had collagenous colitis. The clinical characteristics of affected patients are shown in **Table 1**. There was a clear female predominance of affected patients (74.3% females). All patients were diagnosed in the adult age (18 years and above). We had two patients whose symtoms started in the adolescence (14 and 16 years). All patients suffered from diarrhea as chief symptom, followed by abdominal pain, weight loss, bloating, fatigue, nausea / vomiting. Typical risk factors for microscopic colitis such as statins (HMG-CoA reductase inhibitors), non-steroidal anti-inflammatory drugs, proton-pump inhibitors, or smoking were frequently found. Median exposure time to these risk factors was 55 months. Concomitant allergies were described in 25/2018 (11.5%) of patients (16 patients with seasonal rhinoconjunctivitis, 5 patients with asthma, 4 patients with neurodermitis, and one patient with food allergies against red fruits and mushrooms). None of the patients had a positive history with another family member affected by microscopic colitis. Infectious agents were searched and excluded as cause of chronic diarrhea in all included patients.

The endoscopic and histologic characteristics of patients with microscopic colitis at the time of diagnosis are shown in **Table 2**. A colonoscopy was performed as diagnostic tool in all of the 218 patients. In the majority of patients (74.3%) the

colonoscopy was normal. There was no colorectal cancer found in patients with microscopic colitis and neither an association with Crohn's disease or ulcerative colitis.

Endoscopic abnormalities were described as edema (9.2%) and erythema (4.6%). Median thickness of the subepithalial collagen band in patients with collagenous colitis was 25µm, whereas patient with lymphocytic colitis had a median of 35 intra-epithelial lymphocytes per 100 epithelial cells.

Incidence and prevalence of microscopic colitis over time

Incidence rates were calculated and are shown together with the cumulative prevalence in **Table 3**. No patient was diagnosed with microscopic colitis prior to 1994. Incidence of microscopic colitis significantly increased from 0.36/100,000 inhabitants in 1994-1997 to 6.85/100,000 inhabitants in 2017 (p=0.025, trend test). The cumulative prevalence of microscopic colitis, lymphocytic colitis, and collagenous colitis in 2017 was 19.65/100,000, 11.09/100,000, and 8.56/100,000, respectively. Incidence and prevalence of microscopic colitis, lymphocytic colitis, and collagenous colitis respectively are further shown in **Figure 1** and **Figure 2**. As such, the current prevalences for microscopic colitis, lymphocytic colitis, and collagenous colitis are 1/5,088 persons, 1/9018 persons, and 1/11,676 persons, respectively.

Therapy of microscopic colitis and natural history

Therapies used to treat microscopic colitis are shown in **supplementary Table 1**. Oral budesonide was most frequently used as first therapy, followed by loperamide, aminosalicylates, and cholestyramine. The first applied therapie(s) was/were considered by the treating gastroenterologist as clinically successful for the treatment of microscopic colitis, lymphocytic colitis, and collagenous colitis in 170/218 (78%), 98/123 (79.7%), and 72/95 (75.8%), respectively.

Regarding therapies ever used, oral budesonide was most frequently applied, followed by loperamide, bile acid binders, and probiotics.

When looking at the drugs applied during latest follow-up, we found that 75% of patients had no therapy, followed by loperamide, oral budesonide, aminosalicylates, and bile acid binders.

Median duration of follow-up was 4 years (IQR 2-7, range 1-22 years) for patients with microscopic colitis. The results on disease evolution are shown in **Figure 3**. We found that 62% of patients had a mild disease, wheras 28% of patients showed moderate disease activity and only 10% of patient had chronic ongoing disease. Stopping the offending factor (eg. smoking, statins, etc) was the only factor significantly associated with a mild disease course (**supplementary Table 2**).

DISCUSSION

Our population-based study from a geographically confined region with roughly 1 million inhabitants in the Western part of Switzerland carries several messages that are clinically relevant. First, we observed a steady increase in incidence and cumulative prevalence of microscopic colitis during the last two decades. Second, two thirds of affected patients show a mild disease course, as such, the use of immunomodulators or biologics was rarely necessary. And third, stopping the offending agent was significantly associated with a mild disease course.

Reported incidences of our population-based study are in accordance with already published literature that documented incidences ranging from 2.3 to 16/100,000 for lymphocytic colitis and 2.0 to 10.8/100,000 for collagenous colitis.[10-16] However, the cumulative prevalence for microscopic colitis in our study (19.7/100,000 in the 2014-2017 period) is lower compared to the one of the Orebro area in Sweden which was 123/100,000.[13] This difference in cumulative prevalence can be explained by the fact that in Sweden microscopic colitis was already described in 1984 whereas in our cohort the entity was only described in 1994.[4] Bergman and coworkers recently published results of the first nationwide cohort to assess the incidence of microscopic colitis in Sweden from 1995-2015. Among 13,844 patients, incidence of microscopic colitis was 10.5/100,000 as from 2006 which is rougly 6 times higher comparable to our results.[17] Authors further described a constantly increasing incidence of microscopic colitis over time which we found as well.[17] Our data are comparable with the results of

Fernandez-Banares and coworkers who found lower incidences (2.2/100,000 for lymphocytic colitis and 2.6/100,000 for collagenous colitis) in the period between 2004-2008 in a mixed rural-urban catchment area of 290,000 inhabitants in Spain.[18] These results reinforce the existence of a north-south gradient of microscopic colitis which has been described by several groups.[1,2,4-6,8-10,14]

With regards to the clinical presentation, the results of our study are congruent to the findings of other research groups. In fact, older age at diagnosis and female preponderance have been reported by several authors.[10-18] In a meta-analysis from Tong and coworkers published in 2015, female preponderance was more pronounced in patients with collagenous colitis compared with lymphocytic colitis which we found as well (83.2% females with collagenous colitis versus 67.5% females with lymphocytic colitis, p=0.009).[19] Comparably to the published literature, we identified diarrhea and abdominal pain as chief symptoms of patients with microscopic colitis.[4-11,20,21] We identified 2.3% of patients with microscopic colitis to have associated celiac disease. These results range within the published prevalence of microscopic colitis associated celiac disease between 2 to 9%.[22,23] Utilization of different drugs, such as aspirin or statins, is regarded as risk factor for microscopic colitis. The frequency of drugs associated with microscopic colitis in our cohort is in accordance with published literature.[1-8] Smoking is associated as well with an increased risk of developing microscopic colitis.[24,25] In our cohort, 20.2% of patients with microscopic colitis were smoking at diagnosis. As such, the smoking prevalence is lower compared

to the cohort of Vigren and coworkers who documented 37% of smokers among their patients.[25]

The primary goal of management in patients with microscopic colitis is to achieve clinical remission and to improve quality of life. As of yet histologic remission has not been identified as clinically relevant treatment target. Active disease is defined as ≥3 stools daily or ≥1 watery stool daily.[1,3] Offending agents for microscopic colitis, such as distinct drugs mentioned above and also smoking should be avoided.[26] In our cohort, oral budesonide was most frequently used as first therapy (72.9% of patients) as well as therapy every used (86.2%) to treat patients with microscopic colitis. These data are well in accordance with the results of several randomized, placebo-controlled clinical trials that proved a high response rate using oral budesonide for treatment of microscopic colitis.[27-31] Loperamide was the second most frequently used drug in our patients, although it has never been formally tested in this particular indication by randomized placebo-controlled trials.[1] Loperamide was more frequently used in our cohort when compared to the study of Olesen and coworkers (loperamide use in 33.7% of patients) and Bohr and coworkers (loperamide use in 42.3% of patients).[5,16] Aminosalicylates were ever used in 36.6% of patients with lymphocytic colitis and 30.5% of patients with collagenous colitis although mesalamine did not prove to be superior to placebo as induction therapy.[32] Additional evidence on the lack of efficacy of aminosalicylates was provided by a recently published randomized, placebo-controlled, multicenter study that evaluated 9mg oral budesonide versus 3gr oral mesalazine versus

placebo as induction therapy for lymphocytic colitis.[33] Authors found that 79% of patients in the budesonide group were in clinical remission at week 8 compared to 63% of patients in the mesalazine group and 42% of patients under placebo (p=0.09 between mesalazine group versus placebo). Immunomodulators or anti-TNF agents were ever used in only 7.4% of our patients. Limited evidence from small case series and retrospective studies suggest that these drugs can indeed induce remission in patients with refractory microscopic colitis.[34-36]

Microscopic colitis is characterized by a chronic, intermittent course in most patients.[37,38] Diarrhea may resolve within weeks with or without treatment, but relapses are common.[37-39] Over a median follow-up duration of 4 years, we found that 62% of patients with microscopic colitis had a mild disease course whereas 28% of patients showed moderate disease activity and only 10% had chronic ongoing disease. Our results on the natural history are comparable with the above cited literature.[37-39]

Our study has several strengths and also some weaknesses. We present the first population-based study on incidence and prevalence of microscopic colitis in Switzerland in a reference population of 1.1 million inhabitants. All gastroenterologists and pathologists working in Cantons of Vaud and Fribourg collaborated in this project which is crucial for the generation of population-based data. A thorough chart review allowed the assessment of clinical presentation, associated risk factors, and follow-up over a median of 4 years. As a first limitation, we could not systematically assess the rate of colonoscopies with or

without biopsies starting 1994 in the entire catchment area as this information was not available by all gastroenterologists. This information would be interesting in order to understand how the increasing incidence of microscopic colitis associates with the number of colonoscopies. Second, the first cases with microscopic colitis in our catchment area were only described in 1994 which is 10 years later compared to the description of the first cases in Sweden.[4] This observation might be explained by insufficient awareness of microscopic colitis by gastroenterologist and pathologists alike in the 1980's. As a third limitation the natural history of microscopic colitis was determined by retrospective chart review, completed if necessary by telephonic patient interviews. It is possible that mild flares were handled by patients themselves and thus the actual flare rate would likely be under-represented. Lastly, the use of over the counter drugs such as NSAID or aspirin might be underrepresented.

In conclusion, we present results of the first Swiss population-based study on microscopic colitis. We observed a steady increase in incidence and cumulative prevalence during the last two decades. Our results show a benign disease evolution in roughly 60% of patients. Stopping of factors associated with microscopic colitis was associated with mild disease course.

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Author contributions

HM and AS planned the study. HM, ES, SG, CS, PY, HB, WS, ES, LT, FS, and AS collected, assembled, analyzed, and interpreted the data. HM, ES, and AS drafted the manuscript. HM, ES, SG, CS, PY, HB, WS, ES, LT, FS, and AS revised the manuscript and approved its final version. AS supervised the study.

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Conflict of interest relevant to this study: none for all authors

FIGURE LEGEND:

Figure 1: Incidence rates of microscopic colitis, lymphocytic colitis, and collagenous colitis per 100,000 inhabitants between 1994 and 2017.

Figure 2: Prevalence of microscopic colitis, lymphocytic colitis, and collagenous colitis per 100,000 inhabitants between 1994 and 2017.

Figure 3: Disease evolution over a median follow-up time of four years. Mild disease was characterized by less than one flare per year whereas moderate disease was defined by at least one flare per year and severe disease as chronic ongoing disease.

Supplementary Figure 1: Patient flow

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TABLES

Table 1: Clinical characteristics of microscopic colitis patients. Abbreviations: NSAID, non steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitors.

Item	**Microscopic colitis (n=218)**	**Lymphocytic colitis (LyC) (n=123)**	**Collagenous colitis (CC) (n=95)**	**p-value (CC vs. LyC)**
Female gender	162 (74.3%)	83 (67.5%)	79 (83.2%)	0.009
Provenience - Vaud - Fribourg	 170 (78%) 48 (22%)	 93 (75.6%) 30 (24.4%)	 77 (81.1%) 18 (18.9%)	 0.336 0.336
Age at first symptoms (years)	62.0±15.4, 24-89	61.7±15.1, 24-89	62.4±15.8, 6-90	0.742
Age at diagnosis of microscopic colitis (years)	63.2±14.3, 29-89	62.8±14.3, 27-89	63.7±14.4, 34-91	0.615
Diagnostic delay (years)	0, 0-1, 0-14	0, 0-1, 0-14	0, 0-1, 0-32	0.458
Body mass index at diagnosis (kg/m2)	24.5, 21.7-28, 14.4-34.5	24.5, 21.9-27.9, 18.2-31.2	25.8, 20.9-30, 14.4-34.5	0.885
Symptoms leading to diagnosis - Diarrhea - Abdominal pain - Weight loss - Bloating - Fatigue - Nausea/ Vomiting	 218 (100%) 69 (31.7%) 68 (31.2%) 45 (20.6%) 21 (9.6%) 7 (3.2%)	 123 (100%) 39 (31.7%) 37 (30.1%) 21 (17.1%) 10 (8.1%) 5 (4.1%)	 95 (100%) 30 (31.5%) 31 (32.6%) 24 (25.3%) 11 (11.6%) 2 (2.1%)	 NA 0.984 0.687 0.139 0.392 0.416
Risk factors - statins - NSAID	 59 (27.1%) 31 (14.2%)	 29 (23.6%) 15 (12.2%)	 30 (31.6%) 16 (16.8%)	 0.187 0.330

- PPI	49 (22.5%)	21 (22.1%)	28 (29.5%)	0.029
- SSRI	49 (22.5%)	24 (19.5%)	25 (26.3%)	0.233
- smoking	44 (20.2%)	27 (21.9%)	17 (17.9%)	0.459
- Aspirin	51 (23.4%)	24 (19.5%)	27 (28.4%)	0.123
- Neuroleptics	9 (4.1%)	5 (4.1%)	4 (4.2%)	0.957
- Anti-Parkinson drugs	3 (1.4%)	2 (1.6%)	1 (1.1%)	0.719
Exposure time to risk factors (months)	55, 33-78, 1-280	53, 19.5-82, 1-350	57, 40-72, 3-240	0.893
Associated auto-immune diseases				
- Celiac disease	5 (2.3%)	3 (2.4%)	2 (2.1%)	0.870
- Type 1 diabetes	2 (0.9%)	0	2 (2.1%)	0.106
- Autoimmune gastritis	1 (0.5%)	1 (0.8%)	0	0.378
- Autoimmune thyroiditis	5 (2.3%)	1 (0.8%)	4 (4.2%)	0.097
- Rheumatoid arthritis	2 (0.9%)	1 (0.8%)	1 (1.1%)	0.854

Table 2: Endoscopic and histologic presentation of microscopic colitis patients overall and stratified into lymphocytic colitis and collagenous colitis. Abbreviation: IEL, intra-epithelial lymphocytes; NA, not applicable.

Item	**Microscopic colitis (n=218)**	**Lymphocytic colitis (LyC) (n=123)**	**Collagenous colitis (CC) (n=95)**	**p-value (CC vs. LyC)**
Endoscopic appearance				
- Normal	162 (74.3%)	95 (77.2%)	67 (70.5%)	0.261
- Polyps	36 (16.5%)	19 (15.4%)	17 (17.9%)	0.629
- Edema	20 (9.2%)	12 (9.8%)	8 (8.4%)	0.735
- Erythema	10 (4.6%)	5 (4.1%)	5 (5.3%)	0.675
- Erosion(s)	1 (0.5%)	0	1 (1.1%)	0.254
Histological presentation				
- Subepithelial collagen band	NA	NA	25, 20-35, 15-60	NA
- IEL per 100 epithelial cells	NA	35, 25-50, 22-80	NA	NA
Histologic diagnosis of MC established in biopsies of				
- Right colon, transverse, left colon	174 (79.8%)	104 (84.6%)	71 (74.7%)	0.071
- Right colon only	34 (15.6%)	14 (11.4%)	20 (21.1%)	0.051
- Right colon and left colon	4 (1.8%)	3 (2.4%)	0	0.125
- Transverse and left colon	1 (0.5%)	1 (0.8%)	0	0.378
- Left colon only	5 (2.3%)	1 (0.8%)	4 (4.2%)	0.097

Table 3: Incidence (plus 95% confidence intervals) and prevalence of microscopic colitis (MC), lymphocytic colitis (LyC) and collagenous colitis (CC) from 1994 to 2017. The incidence is shown per 100,000 inhabitants, stratified according to 4 year intervals and per year. The prevalence was calculated per 100,000 inhabitants at the end of the time respective 4 year interval.

Interval	**1994-1997**	**1998-2001**	**2002-2005**	**2006-2009**	**2010-2013**	**2014-2017**
Population Vaud + Fribourg	839,965	856,091	901,168	967,802	1,027,985	1,109,230
Microscopic colitis new cases	3	8	22	45	64	76
Microscopic colitis incidence per 4 year interval	0.36, 0-0.48	0.93, 0.48-1.4	2.44, 2.2-2.68	4.7, 3.32-5.8	6.23, 5.44-7	6.85, 6.12-7.56
Microscopic colitis incidence per year	0.09	0.23	0.61	1.18	1.56	1.71
Microscopic colitis prevalence	0.36	1.29	3.66	8.06	13.81	19.65
Lymphocytic colitis new cases	1	5	16	27	35	39
Lymphocytic colitis incidence per 4 year interval	0.12, 0-0.48	0.58, 0.48-0.92	1.78, 1.32-2.2	2.79, 2.48-3.32	3.41, 2.72-3.88	3.52, 2.88-3.96
Lymphocytic colitis incidence per year	0.03	1.5	0.45	0.7	0.85	0.88
Lymphocytic colitis prevalence	0.12	0.7	2.44	5.06	8.17	11.09
Collagenous colitis new cases	2	3	6	18	29	37

Collagenous colitis incidence per 4 year interval	0.24, 0-0.48	0.35, 0-0.48	0.67, 0.48-0.89	1.86, 1.24-2.48	2.92, 2.72-3.12	3.34, 2.88-3.6
Collagenous colitis incidence per year	0.06	0.09	0.17	0.47	0.73	0.84
Collagenous colitis prevalence	0.24	0.58	1.22	2.99	5.64	8.56

SUPPLEMENTARY TABLES

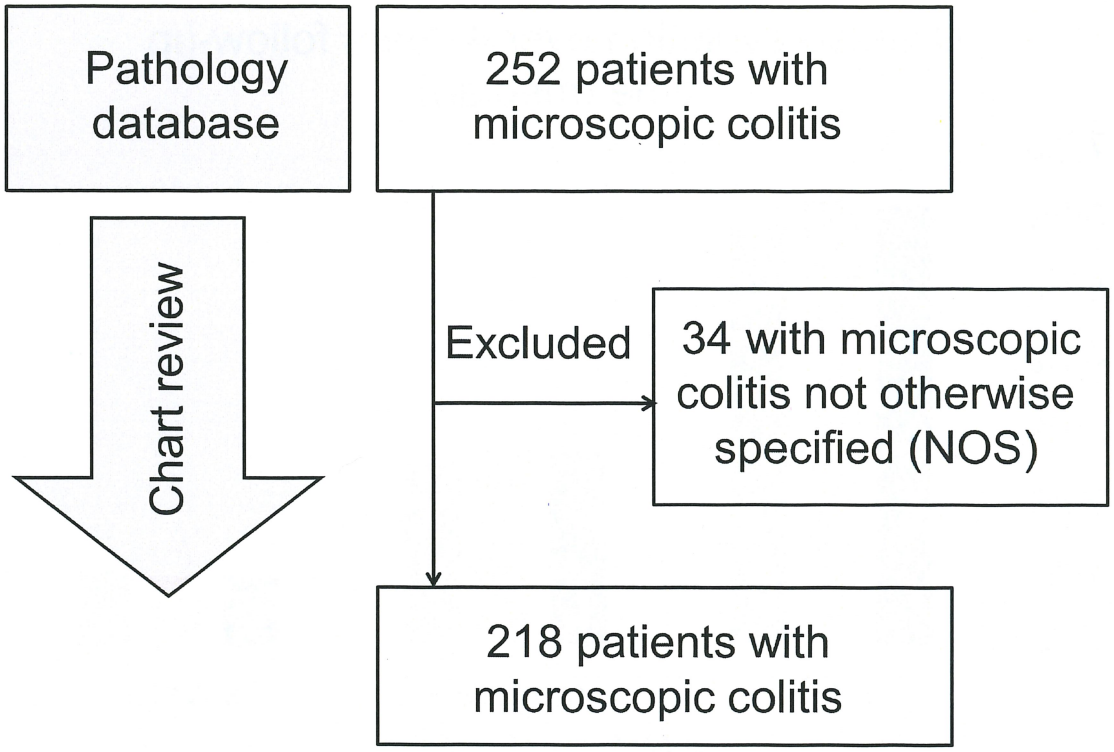
Supplementary Table 1: First therapy, therapies ever applied, and therapies during latest follow-up to treat patients with microscopic colitis, lymphocytic colitis, and collagenous colitis.

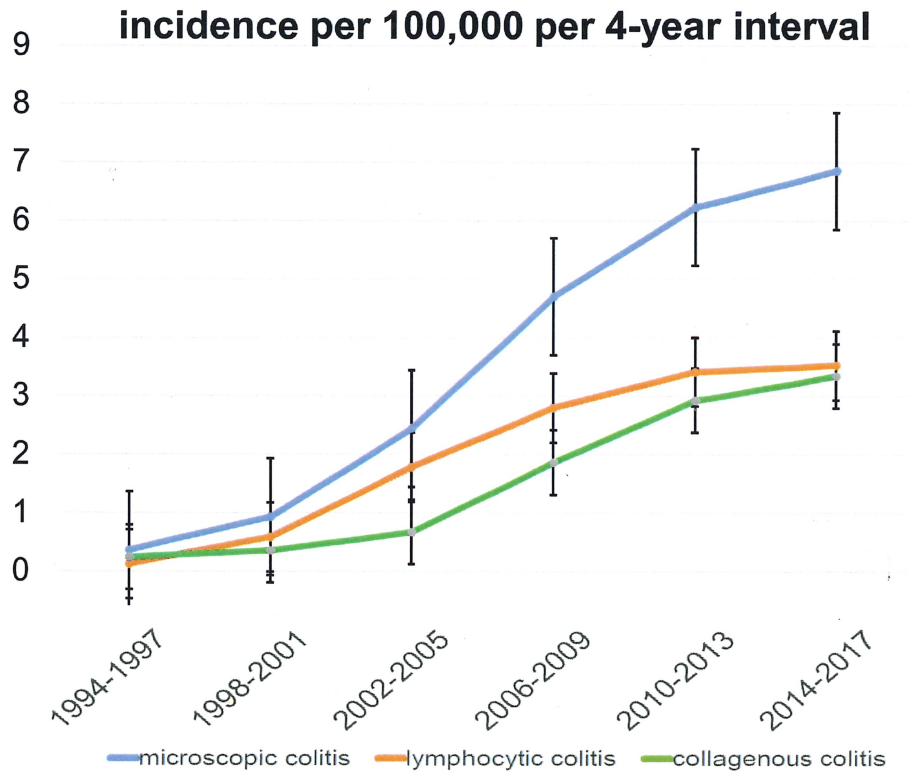
Item	Microscopic colitis (n=218)	Lymphocytic colitis (LyC) (n=123)	Collagenous colitis (CC) (n=95)	p-value (CC vs. LyC)
First therapy applied				
None	8 (3.7%)	4 (3.3%)	4 (4.2%)	0.740
Loperamide	144 (66.1%)	85 (69.1%)	59 (62.1%)	0.134
Aminosalicylates	35 (16.1%)	19 (15.4%)	16 (16.8%)	0.851
Probiotics	6 (2.8%)	2 (1.6%)	4 (4.2%)	0.262
Cholestyramine	28 (12.8%)	17 (13.8%)	11 (11.6%)	0.566
Oral budesonide	159 (72.9%)	95 (77.2%)	64 (67.4%)	0.025
Prednisone	7 (3.2%)	4 (3.3%)	3 (3.2%)	0.939
Azathioprine	0	0	0	NA
Methotrexate	0	0	0	NA
Anti-TNF	0	0	0	NA
Octreotide	0	0	0	NA
Surgery (ileostomy or colostomy)	0	0	0	NA
Therapy ever used				
None	0	0	0	NA
Loperamide	180 (82.6%)	101 (82.1%)	79 (83.2%)	0.840
Aminosalicylates	74 (33.9%)	45 (36.6%)	29 (30.5%)	0.349
Probiotics	11 (5%)	5 (4.1%)	6 (6.3%)	0.452
Cholestyramine	52 (23.9%)	29 (23.6%)	23 (24.2%)	0.913
Oral budesonide	188 (86.2%)	103 (83.7%)	85 (89.5%)	0.223
Prednisone	10 (4.6%)	5 (4.1%)	5 (5.3%)	0.675
Azathioprine	8 (3.7%)	5 (4.1%)	3 (3.2%)	0.724
Methotrexate	3 (1.4%)	3 (2.4%)	0	0.125
Anti-TNF	5 (2.3%)	4 (3.3%)	1 (1.1%)	0.282

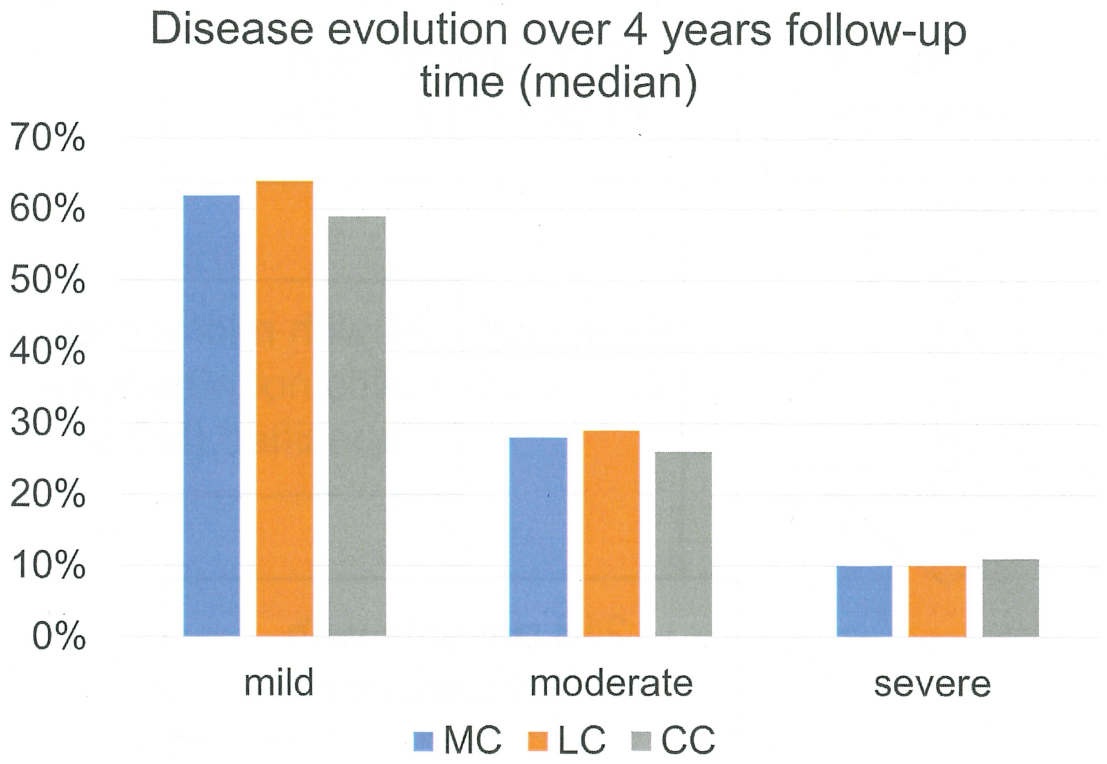
Octreotide	0	0	0	NA
Surgery (ileostomy or colostomy)	0	0	0	NA
Therapy at latest follow-up				
None	145 (75.1%)	86 (77.5%)	59 (72%)	0.380
Loperamide	27 (14%)	15 (13.5%)	12 (14.6%)	0.824
Aminosalicylates	17 (8.8%)	9 (8.1%)	8 (9.8%)	0.689
Probiotics	0	0	0	NA
Cholestyramine	8 (4.1%)	6 (5.4%)	2 (2.4%)	0.307
Oral budesonide	24 (12.4%)	15 (13.5%)	9 (11%)	0.597
Prednisone	1 (0.5%)	1 (0.9%)	0	0.389
Azathioprine	5 (2.6%)	3 (2.7%)	2 (2.4%)	0.909
Methotrexate	1 (0.5%)	0	1 (1.2%)	0.243
Anti-TNF	0	0	0	NA
Octreotide	0	0	0	NA
Surgery (ileostomy or colostomy)	0	0	0	NA

Supplementary Table 2: Univariate and multivariate logistic regression to identify factors associated with a mild disease course, which was defined as less than one flare per 12 months follow-up time. Abbreviations: OR, odds ratio; 95%-CI, 95% confidence interval.

Item	**Univariate model**			**Multivariate model**		
Item	**OR**	**95%-CI**	**p**	**OR**	**95%-CI**	**p**
Stop of offending agent	3.11	1.27-7.59	0.013	3.13	1.28-7.66	0.013
Female gender	0.89	0.48-1.65	0.728			
Lymphocytic colitis	1.65	0.96-2.86	0.072	1.07	0.46-2.51	0.872
Exposure time to offending factor (months)	0.99	0.99-1.01	0.780			


Pathology database
252 patients with microscopic colitis
Chart review
Excluded
34 with microscopic colitis not otherwise specified (NOS)
218 patients with microscopic colitis


incidence per 100,000 per 4-year interval
9
8
7
6
5
4
3
2
1
0
1994-1997
1998-2001
2002-2005
2006-2009
2010-2013
2014-2017
microscopic colitis
lymphocytic colitis
collagenous colitis


Disease evolution over 4 years follow-up time (median)
70%
60%
50%
40%
30%
20%
10%
0%
mild
moderate
severe
MC
LC
CC