

The Association between Microscopic Colitis and Celiac Disease: A Systematic Review

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Abstract

Chronic diarrhea is a symptom of the inflammatory condition known as microscopic colitis (MC) a microscope showing signs of persistent inflammation but with normal colonic morphology under a microscope. The study looked at how common CD was among MC patients, various characteristics of these 2 ailments, as well as the possible association between CD and MC with its two types by analyzing previously available literature. The papers were selected using the EBSCO Information Services and the PubMed database. All essential articles pertaining to both our topics Several more works were consulted for this evaluation. Not included were any other articles that are unrelated to this topic. The group members examined the data that had been extracted in a specific format. both MC types have a sizable CD frequency, this comprehensive Analysis shows that CD and MC have a statistically significant association with an elevated risk of current and past MC in CD patients. When assessing patients with any condition, GI specialists should be cautious of this relationship.

Keywords: Microscopic colitis, Celiac disease, Lymphocytic colitis, Collagenous colitis, Autoimmune disease, Diarrhea

INTRODUCTION

Chronic diarrhea is a symptom of the inflammatory condition known as microscopic colitis (MC) a microscope shows signs of persistent inflammation but with normal colonic morphology under a microscope [1]. The first mention of MC was made by Read *et al.* in 1980. as a potential cause of chronic diarrhea with an unidentified etiology [2]. The characteristic of MC is watery, non-bloody diarrhea, although other signs and symptoms, like fatigue, Additionally recognized symptoms include weight loss and stomach pain. Depending on the results of a colonic biopsy's histopathology, Collagenous colitis (CC) and lymphocytic colitis (LC) are two common classifications for the illness [3]. Intraepithelial lymphocyte counts that rise to at least >20 per 100 cells while preserving the structural integrity of the crypts are the hallmark of LC. LC is inferior to, CC and possesses a subepithelial collagen band with a width of more than 10 micrometers (m) [4, 5]. Since the clinical presentation, assumed pathogenesis and clinical course of the two variations are similar [6], they were subsequently combined into a single disease entity, MC.

MC is a prevalent condition. Tong *et al.*'s meta-analysis revealed CC and LC had combined incidence rates of 4.14 and 4.85 per 100,000 person-years, respectively. According to an identical study, women are more likely than men to develop MC, which has an incidence ratio of 1.92:1 for LC and 3.05:1 for CC. For both CC and LC, the median age of onset is roughly 65 years old and 62 years old, respectively. [7]. There is still much to learn about the precise

pathophysiology and progression of MC. Koskela *et al.* proposed a strong link between MC and autoimmune lymphocytic disorders, including CD [1].

Gluten is a trigger for the autoimmune condition celiac disease (CD) consumption causes small intestine inflammation, leading to villous atrophy [3, 8]. Fatigue, stomach pain, weight loss, and diarrhea are common signs of CD. The histological examination of intestinal tissue, clinical signs, and serological indicators samples are used to identify CD [9]. Histological analysis often reveals a continuum of illness, from increased epithelium apoptosis to complete mucosal degradation marked by villi hyperplasia and loss, villi shrinkage, and intraepithelial lymphocytosis [10, 11]. Gluten antigen, which is primarily found plays a part in CD pathogenesis when it is present on the surface of HLA complexes with the DQ2 or DQ8 haplotype [12].

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According to a systematic study and meta-analysis published in 2018, CD affects 1.4% of the world's population [3].

Although there have been reports of a relationship between CD and MC, there are not many adequately powered cohort studies that span a wide range of layers, and they are highly generalizable. A recent case-control study from Denmark that included 42 exposures and 180 patients with MC found an odds ratio of 10.1. Even though this finding is consistent with the literature, the study was limited because it only used unreliable histological data for MC. Additionally, as connections to 42 different exposures were looked into, multiple testing may have an impact [13].

The link between CD and MC was investigated in two studies: one from a single Canadian center in 2011 and the other from a tertiary center in New York in 2009. Canadian research [14] compared to the American study, which showed a normalized incidence ratio of 52.7. [15] found that CD had a 70-fold higher risk of MC than the overall population. MC was present in 4.5% of patients with refractory CD, according to a thorough review and meta-analysis from 2021. [16] based on five research investigations including 2589 participants.

Although it has been shown by numerous research that MC and CD exhibit a strong association and share a common pathophysiological course, these investigations were constrained by their small sample numbers or areas of interest [17]. It may be necessary to investigate the relationship between MC and CD to screen for related pathologies or modify patients how are managed, especially if they don't respond to first-line treatment. If such immune-mediated diseases are shown to be related. Therefore, the relationship between CD and MC is extensively investigated in this work.

Study Objective

This study's primary goal is to review the most recent published research on microscopic colitis, celiac disease and the association between them.

MATERIALS AND METHODS

Exploratory research using a quantitative technique is part of this integrative literature review (ILR). ILR is a method for gathering prior research to synthesize information on a subject; In the health sciences, it is widely used to pinpoint new treatments and determine advancements, ensuring quality, encouraging patient safety, and permitting the use of evidence-based treatments.

Due to their standing as trustworthy sources, the publications utilized in the study were found using the search engines PubMed and EBSCO Information Services. The National Center for Biotechnology Information (NCBI) produced PubMed, one of the largest online digital libraries.

a department inside the US National Library of Medicine. The theme of eating disorders was used in the writing of the paper. The founded articles' headings and summaries were examined. Articles were chosen for inclusion based on their applicability to the study, which should have dealt with celiac disease, microscopic colitis, lymphocytic colitis, or collagenous colitis. All additional works that did not focus on one of these subjects, as well as repeated research and reviews of studies, were disqualified.

No software was used for the data analysis, according to statistics. The information was extracted using a specified form that contained the publication's title, the author's name, the purpose, and overview, findings, and conclusions). To ensure validity and reduce errors, the results of each member were double-revised.

Studies were peer-reviewed twice during the selection of papers, and their findings to ensure that we enroll studies that are relevant to our study's goal and to prevent or reduce inaccuracies in the results.

RESULTS AND DISCUSSION

The choice and naming of studies are shown in **Figure 1**. A total of 215 studies were found after searching the aforementioned databases, which were then used for title screening. Of those, 60 were selected for abstract review. It resulted in 35 articles being excluded. The whole texts of the final 25 publications were examined. Due to different inclusion criteria following the full-text revision, 19 studies were excluded, and only six were chosen to participate in the final data extraction (**Tables 1 and 2**). Between 2009 and 2023, many studies demonstrate microscopic colitis and celiac disease are related. four studies are only mentioned in this article, some of them are clinical trials and others are prospective studies and case reports.

In this methodical investigation, we discovered a link between celiac disease and the two kinds of microscopic colitis. According to Bergman, *et al.*, [3] a large number of CD patients were included in a nationwide matched cohort study that was conducted in 2023. It is acknowledged that CD patients receive MC diagnoses earlier than other populations. Furthermore, Green, Peter H R, *et al.*, 2009 [15] study demonstrated the same principle as patients with celiac disease have a higher prevalence of microscopic colitis than the overall population. It was also reported that people with celiac disease and microscopic colitis have more severe villous atrophy and frequently require the use of steroids or immunosuppressant drugs to treat diarrhea.

Nimri, Faisal M, *et al.*, 2022 [18] developed a study that included a systematic review and meta-analysis. included all relevant observational findings and studies that suggested a relationship between MC and CD. According to the data from this study, patients with CD had a rate of MC of 6.7%, whereas those without CD had a rate of 7.7%. Both forms of

MC had high CD rates: 5.4% for CC and 9.1% for LC. The largest cross-sectional investigation among these studies was conducted by Sonnenberg *et al.*, in 2018 [19], encompassing 1864 patients who had the LC subtype, 1864 patients who had the CC subtype, and 1592 patients had 3456 patients with MC. A correlation between CD and MC has been proposed by other investigations that have identified comparable HLA complexes implicated in the onset of both disorders. Some of the gathered data have revealed that the diseases have very comparable immunological developments because It is still unclear what causes the relationship between MC and CD in the first place [18].

Dias Antunes, Joana *et al.* 2022 [20] conducted a case report on a female patient, age 65 to demonstrate how a diagnosis of microscopic colitis should be taken into account when celiac patients who have a history of following a consistent gluten-free diet suddenly develop persistent diarrhea.

A total of 86 patients with MC had lymphocytic colitis., and 4 had collagenous colitis, according to Ebik, Berat, *et al.* 2023 [21]. 81.2% of patients are female, and 48.8% did not take any medicine. According to the study, MC was present in 9.3% of patients with persistent diarrhea. Even though studies on his topic revealed significant heterogeneity, 12.8% of individuals with chronic diarrhea are likely to have MC. Only one MC patient was found to have celiac disease. On the other hand, Raju S, Kaur KE, Rawcliffe ME, *et al.* 2022 [22] reported that Clinically and biochemically, patients with MC and CD are identical to patients with CD alone. Patients with concurrent MC and CD, however, frequently present later. The study reported also the first evidence that hospitalized patients with diarrhea and known celiac disease should take early colonic biopsies to detect MC consideration. The Included Studies Had Different Study Designs.

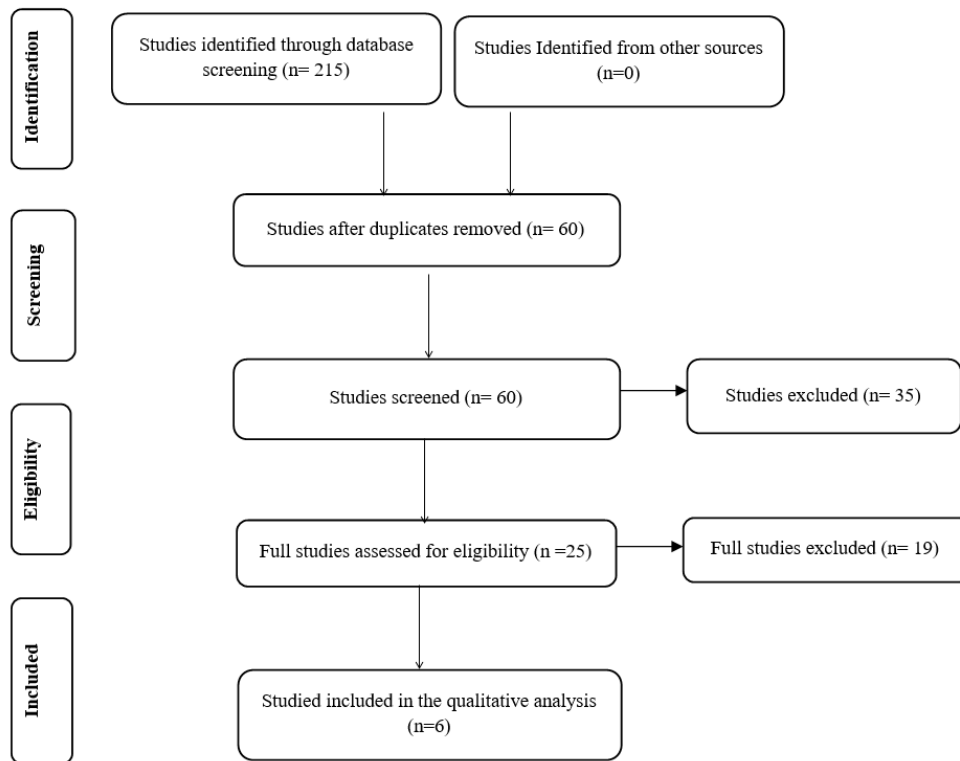


Figure 1. Flow chart illustrates the data extraction process

Table 1. Author, year of publication, nation, gender, study's design, patient count, and the patient population's primary age

Author, year of publication	Country	Study design	No. of patients	Main age	Gender
BERGMAN <i>et al.</i> 2023 [3]	Sweden (1990 – 2016)	nationwide, matched Cohort study	- 51,449 siblings, 223,149 reference people, and 45,138 CD patients	Mean age at diagnosis: 32.4 years	----

Nimri, Faisal M et al. 2022 [18]	---	meta-analysis	26 research with 22,802 participants in total	---	---
Green, Peter H R et al. 2009 [16]	Columbia University in New York (1981 and 2006)	A prospective study	1009 patients	---	64.6% women
Dias Antunes, Joana et al. 2022 [20]	----	Case report	1 patient	65-year-old	Female
Ebik, Berat, et al. 2023 [21]	Turkey September 2011 and December 2021	A prospective, cross-sectional, analytical study	90 patients out of 1096 patients	----	73 females 17 Males
Raju S, Kaur KE, Rawcliffe ME, et al. 2022 [22]	UK January 2014 and December 2020	----	25 patients	median age:61 years	76% female

Table 2. Author, method, and outcomes

Author	Methodology	Outcome
Bergman et al. 2023 [3]	The ESPRESSO project, which details every gastrointestinal biopsy performed in Sweden, is where the information used in this study was gathered. The Systematised Nomenclature of Medicine (SNOMED) system is used to categorize biopsies. Each biopsy in this system receives a unique code based on its histological appearance. Researchers can link information from several healthcare registers thanks to the unique personal identifying number (PIN) that is given to every Swedish resident.	There is a strong relationship between CD and MC both before and after CD was identified. The time of follow-up of the disease plays a role in the risk of MC. Nevertheless, after more than 10 years of follow-ups, the risk was noticeably elevated.
Nimri, Faisal M et al. 2022 [18]	From the beginning through January 2022, a thorough analysis of the databases PubMed, Embase, PubMed Central, Cochrane, and Science Direct was done. The PRISMA guidelines were adhered to when extracting data. In the DerSimonian and Laird generic inverse variance approach, The effect estimates were extracted and combined using pooled odds ratios (OR) and event rates (ER).	CD and MC had a strong relationship. In CD patients, the event rate for MC was 6.2%, whereas the event rate for 6.1% of MC patients had CD. Both kinds of MC had high CD prevalence: lymphocytic colitis had a 6.3% rate and collagenous colitis had a 5.2% rate.
Green, Peter H R et al. 2009 [15]	A celiac disease patient database that was prospectively kept was examined. As the reference group, the creation of standardized morbidity ratios (SMR) involved using a general population study with microscopic colitis. For statistical analysis, one of the following tests was employed: Student t, Pearson chi(2), or Fisher exact.	In comparison to celiac disease patients without microscopic colitis, those were older and had more severe villous atrophy than those with microscopic colitis. In 64% of patients, there was evidence of microscopic colitis. following celiac illness, simultaneously in 25%, and earlier in 11% of individuals.
Dias Antunes, Joana et al. 2022 [20]	A clinical case with a history of both autoimmune hypothyroidism and celiac disease with generalized edema, chronic diarrhea, and unusual weight loss. Fecal calprotectin was detected in a requested fecal analysis. Additionally, an endoscopic examination revealed intestinal villi being flattened. Lymphocytic colitis and celiac disease symptoms were eventually identified by biopsy.	Microscopic colitis is looked at as a potential reason when celiac patients who have a history of adhering to a continuous gluten-free diet exhibit a sudden onset of recurrent diarrhea.
Ebik, Berat, et al. 2023 [21]	In 90 individuals who had colonoscopies and biopsies for chronic diarrhea and were found to have microscopic colitis, the existence of celiac disease was examined.	In individuals who did not undergo colonoscopy for chronic diarrhea, the rate of MC detection was approximately 9.3%. In the colonoscopies ... no pathology was discovered in the biopsies of 465 (42.4%) patients with persistent diarrhea. One (1.1%) of the MC patients who had endoscopic biopsy had CD discovered.
Raju S, Kaur KE, Rawcliffe ME, et al. 2022 [22]	At two hospitals in the UK, case records were found for every patient with histologically proven MC and CD (Group 1) patients. The patients were then contrasted with all adult patients diagnosed with CD at the NHS Coeliac Disease Centre in England (Group 3), who were matched for age and sex and only had Celiac Disease (Group 2).	A median age of 61 years was found among all patients identified in groups 1 and 2, with 76% of them being female. Patients in Group 1 were older at the time of CD diagnosis than those in Group 3 and had the condition before MC. IgA-tTG, IgA-EMA, diarrhea, or HLA type did not differ between Groups 1 and 2.

Lymphocytic colitis and collagenous colitis are two kinds of chronic inflammatory conditions known as microscopic colitis. Histologically, Lamina propria enlargement, chronic

inflammatory cell infiltration, recruitment of intraepithelial lymphocytes, and other characteristics characterize lymphocytic colitis. both superficial injuries to the lamina

propria. Additionally, in cases of collagenous colitis, the sub-epithelial collagen layer thickens [23]. The symptoms of microscopic colitis include urgency, fecal incontinence, and persistent, watery, and non-bloody diarrhea. The majority of patients (50%) complain of abdominal pain, weight loss, and extra-intestinal issues such as arthralgia, arthritis, or uveitis. Anemia The laboratory findings include rheumatoid factor, a high sedimentation rate, and autoantibodies that are present in 50% of patients and include antinuclear, anti-mitochondrial, and anti-neutrophil cytoplasmic antibodies [24]. A well-known autoimmune disorder and food intolerance to dietary gluten is celiac disease. The symptoms include watery diarrhea, steatorrhea, abdominal pain, and weight loss. These symptoms are comparable to those of the other MC, making differential diagnosis involving the other MC an important consideration. A patient may have both illnesses concurrently due to the high association between MC and celiac disease that has been found [23].

A cohort of 21 patients with celiac disease with LC-positive colon biopsies was initially published by Dubois and colleagues in 1989. Since then, several case reports and cohort studies have suggested that CD and MC may be related [25].

It is yet unclear what causes MC and CD to associate with one another. Given that both conditions are linked to increased amounts of specific inflammatory cytokines and indicators, like IFN-, TNF, and IL15, some research has hypothesized that the diseases develop immunologically in remarkably similar ways. Other research has shown similar HLA complexes have been linked to both diseases' beginnings, and a link between CD and MC has been theorized [17].

In the human genome, Westerlind *et al.* and Stahl *et al.* looked at the relationship between MC variants, CC and LC, and particular HLA areas. Researchers found that HLA-DRB104:01 has a protective impact against CC, but patients with certain HLA variations, such as HLA-B08:01, HLA-DRB103:01, and HLA-DQB102:01, have a higher risk of getting the disease. The pathophysiology and immunogenicity of MC were better understood as a result of these findings, and MC may be related to other autoimmune diseases including CD and inflammatory bowel disease, where specific HLA alleles are important or connected to the onset of disease. They claimed that CC and LC may be distinguished by the HLA association, which may disclose variations in pathophysiological development. Later Westerlind *et al.* looked for a connection between LC and certain HLA alleles, such as those with CC, but discovered none [26].

Although CD and MC are in a relationship, the details of that relationship are not clear. Although celiac disease is known to be brought on by an immune cell-mediated response to dietary proteins in genetically susceptible hosts,

the pathogenesis of LC and CC is yet unknown. Fernandez-Banares and others. [27] it is a distinct entity with a variety of pathophysiological mechanisms, it identified. Further complicating matters, small bowel intraepithelial lymphocytosis without overt villous atrophy or CD has been seen in persons with MC and other chronic autoimmune diseases [19].

It was calculated that CD patients have a 70 times higher risk of developing microscopic colitis than the general population. Microscopic colitis is more common in middle-aged women than younger ones [24].

According to a study done by M. Stewart *et al.*, MC prevalence is still rising, indicating that the condition may still be underdiagnosed. It is necessary to talk about the causes of the astonishing rise in LC frequency in men because those factors are still unidentified. Despite being less dramatic than MC, CD is nonetheless becoming more common. especially in women. It is important to emphasize that, rather than an increase in the number of biopsies or procedures carried out, the rise in CD diagnoses is likely caused by an actual rise in the incidence of the illness. Prior research indicates the diagnoses of CD and MC share a lot of similarities. Colonoscopy with biopsies should be performed in middle-aged CD patients, especially if the diarrhea is resistant to a gluten-free diet, to rule out MC [14].

CONCLUSION

The study concludes by showing a strong connection between CD and MC, both before and after CD diagnosis Elderly individuals may encounter incapacitating symptoms that hurt their quality of life, even if major and life-threatening complications are uncommon. more specifically, in female patients reporting MC who have a history of celiac or autoimmune disease, a strong index of suspicion is necessary. Clinicians who treat CD should be aware of these relationships and know when to recommend a colonoscopy. To investigate the connection between these 2 diseases, more research is needed.

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