# Microscopic Colitis in Patients with Unexplained Chronic Watery non-Bloody Diarrhea: A Cross Sectional Study

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**Background and study aim:** Microscopic colitis is an increasingly recognized cause of chronic watery non-bloody diarrhea. The diagnosis of microscopic colitis is mainly based on pathological examination of colonic biopsy from patients with chronic diarrhea and apparently normal colonoscopy examination. This study aimed at estimating frequency of microscopic colitis among patients with chronic watery non-bloody diarrhea and determining the role of some risk factors for its occurrence.

**Patients and Methods:** This study included 60 patients with chronic watery non-bloody diarrhea. Colonoscopy examination was done for all patients and biopsy was taken for histopathology. All patients also evaluated by stool analysis, complete blood count, liver functions, kidney functions, thyroid functions, glycosylated hemoglobin, tissue transglutaminase and pelviabdominal ultrasound.

**Results:** Microscopic colitis was diagnosed in 13 patients with 9 patients having lymphocytic colitis and 4 patients having collagenous colitis. The mean age of patients diagnosed with MC was about 45.7 ± 7.78 years and most of them were females (69.2 %). Patients with microscopic colitis suffered from diarrhea for longer durations. Microscopic colitis was more significant in patients with history of proton pump inhibitors and non-steroidal anti-inflammatory drugs use.

**Conclusion:** Prevalence of microscopic colitis among studied patients was about 21.7% (15% lymphocytic colitis and 6.7% collagenous colitis). microscopic colitis was more common among females .

## INTRODUCTION

Microscopic colitis (MC) is a disease with no established etiology. However, gastrointestinal infections, autoimmune diseases, bile acid malabsorption, and numerous drugs have all been proposed as possible causes for it. MC is frequently missed in diagnosis as most of patients have apparently normal mucosa during colonoscopy examination and it is diagnosed mainly by histopathological examination of colonic biopsy from patients with chronic watery non-bloody diarrhea (CWND) **[1]**.

MC is a growing cause of chronic inflammatory bowel disease, especially in patients presented with watery, non-bloody diarrhea **[2]**. There are two types of MC; lymphocytic (LC) and collagenous colitis (CC) which are characterized by increased inflammatory cells in the surface epithelium and lamina propria in both types and presence of thickened subepithelial collagen layer in collagenous type **[3]**.

The overall incidence rate of MC is about 11.4 patients / 100,000 person-years. The incidence of CC and LC ranges from 0.6 to 16.4 patients / 100,000 person-years and from 0.6 to 16.0 patients / 100,000 person-years, respectively. The frequency of MC in patients with unexplained chronic watery diarrhea is about 12.8% with significant heterogeneity between studies **[4]**.

Epidemiological studies reported an increasing incidence of MC in western countries, and this could be due to genetic, environmental factors or concomitant association with other autoimmune diseases. Geographic variations in the incidence of MC have been recorded; however, the low number of studies from developing countries, make it difficult to determine actual incidence of MC in our region **[5-8]**.

In Egypt, there is a lot of variation in the results of prior studies, and the estimated prevalence of MC in patients with CWND ranges from 10% to 50% **[9-12]**. Infectious gastroenteritis, growing increased incidence of autoimmune diseases and drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and selective serotonin reuptake inhibitors (SSRIs) could be an etiology or risk factor for possible high percentage of MC in developing countries **[13,14]**. The aim of this study is to estimate frequency of MC among patients with CWND in Zagazig University hospitals and to identify the role of some risk factors for its occurrence.

## PATIENTS AND METHODS

**Study design:** It is a cross-sectional study.

**Study settings:** This study was conducted in Tropical Medicine Department, Zagazig University Hospitals, in the period between August 2020 to August 2021. Patients had been recruited from outpatient's clinic of Tropical Medicine Department.

**Study patients:** This study included 60 patients presented to outpatient clinic with CWND. Colonoscopy examination was done for all patients and biopsy taken for histopathology.

**Inclusion criteria:**

- All patients suffered from chronic continuous or intermittent watery non bloody diarrhea of at least three loose motions per day lasting for at least four weeks with no intervening formed or semi-formed motions.
- Patients who showed improvement of motion looseness by using nonspecific stool forming agents was defined as intermittent diarrhea and included in the study.

**Exclusion criteria:**

- Patients with acute or sub-acute diarrhea (less than 1 month duration).
- Patients with evidence of infective cause of diarrhea as chronic giardiasis
- Patients who passed blood or mucus in their stool.
- Patients with steatorrhea (fecal fat more than 7 gm/24 hours after 3 days consumption of 100 gm fat/day with 5 hours fasting before the test).
- Patients who received antibiotics, medical or herbal laxatives.
- Patients with colonoscopy or histopathologic documentation of inflammatory bowel disease and/or colonoscopy finding of ulcer (s), polyp (s) or mass(es).
- Patients with history of gastro-intestinal or pancreaticobiliary operations.
- Patients with major organ failure as live cell failure, chronic renal failure, and heart failure.
- Patients with diabetes or hyperthyroidism.
- Patients who tested positive for human immunodeficiency virus.

**Patient assessment:** All patients were subjected to:

- Full history taking and detailed clinical examination including age, gender, residence and history of drugs intake especially NSAIDs, PPIs and SSRIs. Drugs should be currently used or previously recurrent used during the last 6 – 12 months. Family history of chronic diarrhea or history of autoimmune disease was assessed.
- Laboratory studies included stool examination (to detected blood, polymorph-nuclear cells, fecal fat, or parasitic infestation), complete blood picture, liver function tests, kidney functions tests, glycosylated hemoglobin, thyroid function tests, and tissue transglutaminase to rule out celiac disease.
- Abdominal ultrasonography: Ultrasonography was performed by Esaot Mylab 20 plus to evaluate liver size, spleen size, cecum, and sigmoid wall thickness.
- Total colonoscopy (Pentax EPN 3500 video-colonoscopy): Colonoscopy examination was done for all patients with biopsies collected

from each segment of the colon as well as any abnormally looking areas.

- Histopathological examination: All biopsies were collected and sent to the pathology lab, faculty of medicine, Zagazig University in a 10% formalin solution, which was subsequently processed in paraffin blocks and sliced into 5 m thick unstained slices. Hematoxylin and Eosin and Masson's Trichrome stains are used to stain the slides.

Criteria for histopathological diagnosis of MC included: increased chronic inflammatory cells in the lamina propria, degeneration of surface epithelium, increased intra-epithelial B lymphocytes and increased mitosis in crypts. More than 20 intra-epithelial B lymphocytes per 100 inter-cryptal epithelial cells is required for diagnosis of lymphocytic colitis. A sub-epithelial collagen band thickness more than 10 µm is required for diagnosis of collagenous colitis [15].

**Statistical Analysis**

All data were collected, tabulated, and statistically analyzed using SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as the mean ± SD & median (IQR), and qualitative data were expressed as absolute frequencies (number) & relative frequencies (percentage). Independent samples Student's t-test was used to compare between two groups of normally distributed variables while Mann Whitney U test was used for non- normally distributed variables. Percent of categorical variables were compared using Chi-square test. All tests were two sided. p-value $< 0.05$ was considered statistically significant (S), p-value $\geq 0.05$ was considered statistically nonsignificant (NS).

## RESULTS:

This study included 60 patients presented to outpatient clinic with CWND. Table 1; showed demographic data and history of all patients included in this study. Females represented more than half of the studied patients (58.3%) and the mean age of all patients was about 39.8 years with range from 20 – 70 years. Included patients had no current, past or family history of auto-immune diseases or chronic diarrhea. 53.3 % of patients were resident in urban regions. History of drug intake in included patients was PPIs (46.7 %), NSAIDs (40 %), and SSRIs (21.7 %), respectively. PPIs were prescribed for gastritis, dyspepsia and heart burn. Included patients were given NSAIDs for arthritis, arthralgia or persistent headache. Also, SSRIs was used as treatment for irritable bowel syndrome (IBS).

All studied patients presented with continuous (86.7 %) or intermittent (13.3 %) diarrhea with number of motions/days ranged from 3 – 8 motions/day. There were nocturnal bowel motions, abdominal distension, and no bloody diarrhea in all included patients. The mean duration of chronic diarrhea was about 10 weeks and ranging from 1 - 6 months. 8 patients presented with intermittent nature of chronic diarrhea due to intermittent response to nonspecific stool forming agents.

According to the results of colonoscopy biopsy, patients have been divided into two groups. The first group included 13 patients diagnosed with MC. The second group included 47 patients without MC. The mean age of patients diagnosed with MC was about 45.7 ± 7.78 years and most of them were females (69.2 %). There was a high statistically significant difference between both groups as regard history of chronic use of PPIs and NSAIDs, with the difference being more significant among patients with MC, but no significance difference as regard SSRIs. All MC patients had a history of chronic PPI use, 92.3 % of MC patients had a history of recurrent NSAID use, and 30.8 % of MC patients had a history of SSRIs use (Table 2).

Patients with MC suffered from diarrhea for longer period (mean duration about 4 months) with a high statistically significant difference compared to patients without MC. Diarrhea in all patients with MC was continuous (Table 3). All patients with MC were suffered from abdominal pain, nocturnal diarrhea, and 23% of them had weight loss. Regarding laboratory variables, there is no statistically significant differences between patient with MC and patients without MC as regard CBC parameters, liver function tests, kidney function tests, thyroid function tests and glycosylated hemoglobin (Table 4).

Colonoscopy examination was normal in all patients with no obvious pathological mucosal lesions. Histopathological assessment of colonic biopsies was found to be normal in 78.3% of cases, lymphocytic colitis in 15% of cases, and collagenous colitis in 6.7 % of cases. MC was diagnosed in 21.7 % of studied patients presented with CWND (Table 5).

**Table (1):** Demographic data and history of all the studied patients.

| Variables | | N=60<br>N (%) |
|---|---|---|
| **Age (years)** | Mean ± SD | 39.8±14.1 |
| | Range | 20-70 |
| **Residence** | Urban | 32 (53.3) |
| | Rural | 28 (46.7) |
| **Gender** | Male | 25 (41.7) |
| | Female | 35 (58.3) |
| **Family history of chronic diarrhea** | Yes | 0 (0) |
| | No | 60 (100) |
| **Present, past, or family history of auto-immune diseases** | Yes | 0 (0) |
| | No | 60 (100) |
| **History of use of NSAIDs** | Yes | 24 (40) |
| | No | 36 (60) |
| **History of use of PPIs** | Yes | 28 (46.7) |
| | No | 32 (53.3) |
| **History of use of SSRIs** | Yes | 13 (21.7) |
| | No | 47 (78.3) |

NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, protein pump inhibitors; SSRIs, selective serotonin reuptake inhibitors

**Table (2):** Comparison between the studied groups regarding demographic characteristic and drug history.

| Variables | | Patients with MC<br>N=13<br>N (%) | Patients without MC<br>N=47<br>N (%) | P |
|---|---|---|---|---|
| **Age (years)**<br>Mean ± SD | | 45.7 ± 7.78 | 40.98 ± 15.2 | 0.36*<br>(NS) |
| **Gender** | Male | 4 (30.8) | 21 (44.7) | 0.368†<br>(NS) |
| | Female | 9 (69.2) | 26 (55.3) | |
| **History of use of NSAIDs** | Yes | 12 (92.3) | 12 (25.5) | <0.001†<br>(HS) |
| | No | 1 (7.7) | 35 (74.5) | |
| **History of use of PPIs** | Yes | 13 (100) | 15 (31.9) | <0.001†<br>(HS) |
| | No | 0 (0) | 32 (68.1) | |
| **History of use of SSRIs** | Yes | 4 (30.8) | 9 (19.1) | 0.368†<br>(NS) |
| | No | 9 (69.2) | 38 (80.9) | |

NS: Non significance
HS: Highly significance
*Mann-Whiteny U test
†Chi-square test
MC, microscopic colitis; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, protein pump inhibitors; SSRIs, selective serotonin reuptake inhibitors

**Table (3)**: Characters of diarrhea among both studied groups.

| Variables | | Patients with MC N=13 | Patients without MC N=47 | P value |
|---|---|---|---|---|
| **Number of motions / days** | Mean ± SD | 6 ± 2 | 5 ± 2 | 0.451* (NS) |
| | Median | 4 | 3 | |
| | Range | 4 – 8 | 3 – 8 | |
| **Duration of diarrhea (months)** | Mean ± SD | 4 ± 1.47 | 1.64 ± 0.79 | <0.001* (HS) |
| **Continuity of loose motions** | Continuous | 13 | 39 | 0.499† (NS) |
| | Intermittent | 0 | 8 | |

NS: Non significance
HS: Highly significance
*Mann -Whitney U test.
†Chi-square test.
MC, microscopic colitis

**Table (4):** Comparison between the studied groups regarding laboratory parameters

| Variables | Patients with MC N=13 Mean ±SD | Patients without MC N=47 Mean ±SD | P value |
|---|---|---|---|
| **Hemoglobin(g/dl)** | 12.9 ± 1.38 | 12.1 ± 1.95 | 0.71* (NS) |
| **WBC's (x10$^3$cell/µL)** | 9.8 ± 3.33 | 9.96 ± 3.1 | 0.881* (NS) |
| **Platelet(x10$^3$cell/µL)** | 271.9 ± 45.5 | 251.9 ± 49.6 | 0.184* (NS) |
| **S. albumin (g/dL)** | 4.19 ± 0.72 | 4.3 ± 0.74 | 0.631* (NS) |
| **S. total protein (g/dL)** | 7.02 ± 0.52 | 7.1 ± 0.57 | 0.858* (NS) |
| **T. bilirubin (mg/dL)** | 0.63 ± 0.26 | 0.65 ± 0.27 | 0.801* (NS) |
| **D. bilirubin (mg/dL)** | 0.2 ± 0.08 | 0.17 ± 0.09 | 0.326* (NS) |
| **ALT(IU/L)** | 31.3 ± 5.14 | 29.1 ± 4.95 | 0.177* (NS) |
| **AST(IU/L)** | 28.6 ± 4.98 | 29.4 ± 5.27 | 0.643* (NS) |
| **INR** | 1.04 ± 0.09 | 1.02 ± 0.102 | 0.435* (NS) |
| **S. creatinine (mg/dL)** | 0.87 ± 0.31 | 0.94 ± 0.29 | 0.503* (NS) |
| **S. urea (mg/dL)** | 28.1 ± 6.56 | 29.8 ± 9.1 | 0.445* (NS) |
| **TSH** | 2.1 ± 1.01 | 2.1 ± 1.19 | 0.924* (NS) |
| **T3** | 4.68±2.13 | 4.34±2.2 | 0.01* (S) |
| **T4** | 95.97±14.1 | 91.3±14.9 | 0.301* (NS) |
| **HbA1c (ng\dl)** | 4.82 ± 0.47 | 4.98 ± 0.42 | 0.294† (NS) |

NS: Non significance
S: Significance
* Mann -Whitney U test
†Independent t test
MC, microscopic colitis

**Table (5):** Histopathological finding and prevalence of microscopic colitis among studied patients.

| Variables | | N=60<br>N (%) |
|---|---|---|
| **Biopsy** | Normal | 47 (78.3) |
| | Lymphocytic colitis | 9 (15) |
| | Collagenous colitis | 4 (6.7) |
| **Prevalence** | Microscopic colitis | 13 (21.7) |
| | Normal | 47 (78.3) |

## DISCUSSION

Microscopic colitis is an important cause of chronic watery non bloody diarrhea and accounting for about 10 % of these patients and up to 15 - 20 % of elderly patients **[16]**. Previous studies showed high heterogeneity and are not directly comparable. This could be due to differences in geographical and genetic background, different definitions of chronic watery diarrhea, the lack of clearly defined diagnostic criteria for MC and diagnostic work- up prior to colonoscopy. The aim of this study is to estimate frequency of MC among patients with CWND and to identify the role of some risk factors for its occurrence.

This study showed that more than half of included patients diagnosed with MC were females (69.2%) and mean age was about 45.7 years. These findings agreed with Stoicescu et al., 2012 who showed that the mean age of cases diagnosed with MC was about 45.9 years (range 22.5 - 76) and most of cases were females **[17]**. Similarly, Larsson et al., 2014 showed that most patients with MC were females (77%) **[18]**. However, Fumery et al., 2017 reported that the incidence of MC increased with age, reaching a peak of 28/105 in the eighth decade **[19]**. The present study revealed that there is no relationship between the family history or history of autoimmune diseases and MC. Also, all included patients were negative for celiac disease. However, Stoicescu et al., 2012 diagnosed 6 patients (40%) with MC and associated autoimmune diseases as celiac disease and diabetes mellitus type 1 **[17]**. Also, familial cases of MC have been described **[20]**. This difference could be due to geographical, genetic, or population variations, as most of these studies were conducted in western countries with a high prevalence of autoimmune diseases.

We found that there was strong positive association between patients with MC and the history of use of PPIs and NSAIDs. All MC patients had a history of chronic PPI use, 92.3% of MC patients had a history of recurrent NSAID use, and 30.8 % of MC patients had a history of SSRIs use. In line with our results, many previous retrospective studies had been found a strong association between PPIs usage and MC, especially when used for 4 to 12 months regularly. Prolonged use of NSAIDs was also associated with increased incidence of MC **[21-23]**. The use of both NSAIDs and PPIs together may raise the risk of MC **[24]**. As regard SSRIs, there was no significant association between use of SRRIs and patients with MC in. In contrast, Yen et al., 2017, Guagnozzi et al., 2015 and masclee et al., 2015 reported strong association between SSRIs exposure and MC **[25,21,22]**. This difference could be due to low number of patients with history of SRRIs intake included in our study. It is important to clarify that our study and previous all studies lack information about appearance of clinical symptoms after drug exposure and if symptoms disappear after stopping of drugs in order to establish a causal relationship.

Diarrhea was the main symptom in all patients which was non bloody and watery with mean duration of 4 months in patients diagnosed with MC versus 1.64 months in patients without MC. This finding agreed with Stoicescu et al., 2012 who found that in patients with MC, stool frequency per day was 5/day (range 3 – 12/day) for about 4 months **[17]**. Similarly, Kane et al., 2017 showed 286 patients out of 540 (53.0%) presents with diarrhea more than 1 month duration **[26]**. All patients with MC in our study presented with nocturnal diarrhea, abdominal pain, and 23 % of them had weight loss. However, Stoicescu et al., 2012 reported that nocturnal diarrhea is present in (73.33%) of patients, abdominal pain in 53.33% of patients and slight loss of weight in 40 % of cases **[17]**. Similarly, in a study by Macaigne et al., 2014, abdominal pain had been observed in half of the

patients and loss of weight observed in about 40% of patients **[27]**.

The present study revealed that level of hemoglobin, total leucocytic count, and platelets count was within normal values in patients with MC. Also, there was no statistically significant difference between patients with MC and patients without MC as regard liver function tests, kidney function tests and glycosylated hemoglobin. This agreed with Gustafsson et al.,2013 and Larsson et al.,2014 who showed the same findings in patients with MC **[28,18]**. Regarding thyroid functions, this study showed no abnormalities in thyroid functions in patients with microscopic colitis except for elevated total T3 level which was clinically not significant with normal TSH level in these patients. In contrast, a study by Williams et al., 2008 included 164 patients with MC showed that 18 cases (11%) had previously been diagnosed with hypothyroidism **[20].** In addition, Gustafsson et al., 2013 found that the total prevalence of thyroid abnormalities was greater in patients with MC than in the control sample **[28]**.

Colonoscopy examination of all 60 patients in our study was normal with no obvious pathological mucosal findings and multiple biopsies are taken for histopathology. In consistent with our results, a study by Stoicescu et al. ,2012 which was conducted on 247 patients with no detected any mucosal pathological lesions during colonoscopy examination and had been previously diagnosed IBS with diarrhea **[17]**. In contrast, Mellander et al., 2015 reported endoscopic mucosal abnormalities as oedema, erythema, or abnormal vessel pattern in 37% of collagenous colitis patients and 25% of lymphocytic colitis patients **[29]**. Similarly, Nguyen et al., 2014 showed there are macroscopic endoscopic abnormalities in 20 - 30% of patients with MC **[30]**. This difference between studies could be due to endoscopist-related factors including experience and degree of training, which can influence the detection of subtle endoscopic pathological mucosal abnormalities **[31]**.

In the present study according to histopathological assessment of colonic biopsies, MC was diagnosed in 13 patients (21.7%) with 9 patients' lymphocytic colitis (15%) and 4 patients' collagenous colitis (6.7%). This high prevalence more than western countries could be explained by recurrent infectious gastroenteritis which may disturb gut immune system, growing increases incidence of autoimmune diseases, and prolonged unnecessary drug exposure especially PPIs and NSAIDs. Fernandez et al., 1999 found 23 patients (6%) with collagenous colitis and 37 patients (10%) with lymphocytic colitis among 375 patients evaluated for chronic diarrhea, which is nearly similar to our findings **[32]**. Also, Olesen et al., 2004 studied 1018 patients presented with CWND and coloscopy examination was done, the prevalence of MC was about 20% if only cases more than 70 years old are considered **[33]**.

In Egypt, there was large difference between results of study regarding prevalence of MC. Gado et al., 2011 and Saleh et al., 2016 reported prevalence of MC among patients with chronic watery diarrhea about 50 % and 29.5 %, respectively **[9,10]**, while Gomaa et al., 2017 and Abdelmageed et al., 2020 reported prevalence of MC about 10 % and 14 %, respectively **[11,12]**. This difference may be due to small sample size and population characteristics of included patients. So, large multicenter studies with wide scale are needed to determine the actual prevalence and possible risk factors of MC in Egypt.

This study has some limitations; this study was conducted with a small sample size of patients, which not unable us to find possible associations and differences between subtypes of MC. Patients with lymphocytic colitis and collagenous colitis were considered as a one group in our study as the number of both were small to be compared.

## CONCLUSION

Prevalence of microscopic colitis among studied patients was about 21.7% (15% lymphocytic colitis and 6.7% collagenous colitis). MC was more common among females. Patients with microscopic colitis suffered from diarrhea for longer durations. The use of proton pump inhibitors and non-steroidal anti-inflammatory drugs is an important risk factor for MC development.

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**Conflicts of interest:** None.

**Ethical consideration:**

Permission and official approval to carry out the study was obtained. All patients signed a written informed consent before inclusion into this study and the institutional ethical committee at Zagazig University, Faculty of Medicine approved the study. The study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki.

**Abbreviations:**

MC: Microscopic colitis.

CWND: Chronic watery non-bloody diarrhea.

LC: Lymphocytic colitis.

CC: Collagenous colitis.

NSAIDs: Non-steroidal anti-inflammatory drugs.

PPIs: Proton pump inhibitors.

SSRIs: Selective serotonin reuptake inhibitors.

IBS: Irritable bowel syndrome.

**RESEARCH HIGHLIGHTS**

- Microscopic colitis is an important cause of chronic watery non bloody diarrhea and accounting for about 10 % of these patients and up to 15 - 20 % of elderly patients.
- MC is frequently missed in diagnosis as most of patients have apparently normal mucosa during colonoscopy examination and it diagnosed mainly by histopathological examination of colonic biopsy from patients with chronic watery non-bloody diarrhea.
- Chronic watery non-bloody diarrhea in developing countries require more studies to confirm prevalence of microscopic colitis accurately and to determine risk factor for its development.
- Prevalence of microscopic colitis among studied patients is about 21.7% (15% lymphocytic colitis and 6.7% collagenous colitis). MC is more common among females.
- Patients with microscopic colitis suffered from diarrhea for longer durations. Prolonged use of non-steroidal anti-inflammatory drugs and proton pump inhibitors is an important risk factor for MC development.

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