Microscopic colitis is a risk factor for low bone density: a systematic review and meta-analysis

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Abstract

Background: Microscopic colitis (MC) is a chronic inflammatory disease of the large bowel characterized by watery diarrhea, substantially decreasing the patient's quality of life. Scarce data suggest that MC is associated with low bone density (LBD).

Objectives: We aimed to assess whether MC is a risk factor for LBD and the proportion of patients with MC having LBD.

Design: A systematic review and meta-analysis of studies reporting bone density measurements in MC patients.

Data Sources and Methods: We systematically searched five databases from inception to October 16, 2021 (Pubmed, Embase, Cochrane, Scopus, and Web of Science). We used the random-effect model to calculate pooled odds ratios (ORs) and pooled event rates with 95% confidence intervals (CIs). To ascertain the quality of evidence of our outcomes, we followed the recommendations of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.

Results: The systematic search yielded a total of 3046 articles. Four articles were eligible for quantitative synthesis. All of them used age- and sex-matched controls to evaluate LBD occurrence among patients with MC. The odds of having LBD were twofold increased (OR = 2.13, CI: 1.42–3.20) in the presence of MC, the odds of osteopenia occurrence were 2.4 (OR = 2.45, CI: 1.11–5.41), and of osteoporosis 1.4 (OR = 1.42, CI: 0.65–3.12). The proportion of LBD was 0.68 (CI: 0.56–0.78), osteopenia was 0.51 (CI: 0.43–0.58), and osteoporosis was 0.11 (CI: 0.07–0.16) among the MC population. Our findings' certainty of the evidence was very low following the GRADEPro guideline.

Conclusion: Our data demonstrate that MC is associated with a twofold risk for LBD. Based on our findings, we suggest screening patients for bone mineral density upon diagnosis of MC. Further prospective studies with higher patient numbers and longer follow-up periods on this topic are needed.

Registration: Our protocol was prospectively registered with PROSPERO (CRD42021283392).

Plain language summary

Investigating microscopic colitis as a risk factor for having low bone density in a literature overview and statistical approach

Microscopic colitis (MC) is an underdiagnosed chronic inflammatory large bowel disease, characterized by watery diarrhea, which substantially impacts the patient's quality of life. The etiology of MC is still unclear but is suspected to be multifactorial. Moreover, low bone density (LBD) has been associated with the disease. Scarce data investigate the relationship of MC with LBD, although they share common risk factors, like advanced

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age and female sex. LBD has two forms; the mild is osteopenia and the severe form is osteoporosis. The most severe complications of osteoporosis are osteoporotic fractures, which can culminate in a life-threatening state and amplify the hospital expenses burden. Our primary aim was to assess if MC increases the risk of LBD. Furthermore, we estimated the proportions of bone mineral changes in the MC population.

Following a rigorous methodology, our data suggest that MC doubles the odds of LBD. Furthermore, we have shown that two-thirds of the MC population suffers from bone density decrease, half of them have osteopenia, and one in 10 MC patients has osteoporosis. In conclusion, we highly suggest screening patients with MC for bone mineral density at the moment of diagnosis.

Keywords: chronic inflammation, large bowel disease, low bone density, microscopic colitis, osteopenia, osteoporosis

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Introduction

Microscopic colitis (MC) is a chronic inflammatory large bowel disease, whose precise etiology is still unclear but is suspected to be multifactorial.[1–3] In Europe, MC shows an increased prevalence, approximately 119 per 100,000 persons.[4] Among chronic diarrhea patients undergoing colonoscopy and histopathology, the discovery rate of MC is higher in older women,[5] but younger age manifestations and pediatric cases are also described.[6–8]

MC has a chronic clinical course, which varies from patient to patient, having continuous or recurrent symptoms, lasting from months to years. Although there is increased awareness of the disease, still many patients are symptomatic for years, even decades, until the correct diagnosis is established. The clinical manifestations of MC can be severe, like watery diarrhea, stool incontinence, nocturnal defecation, and weight loss, leading to decreased quality of life.[2]

Numerous risk factors were found to be associated with MC. Although smoking and drugs are the most recognized, the list of these risk factors is extensive and still under debate.[2] There is a lack of data on MC extraintestinal complications too. Scarce publications report bone mineral changes in MC. Chronic watery diarrhea in MC may lead to calcium and vitamin D loss, which ultimately can manifest in osteoporosis or osteoporosis-related fractures.[9] The gold standard therapy of MC is the locally acting steroid budesonide.[10] Budesonide has been implicated in long-term therapy in the development of low bone density (LBD).[11] However, Tome *et al.* demonstrated that during 5.6 years of follow-up of patients on budesonide therapy, there was no significant increase in the incidence of adverse events like osteopenia, osteoporosis, diabetes, hypertension, glaucoma, or cataracts.[12] We hypothesize that MC may lead to secondary osteoporosis.

Osteoporosis is a universal disease; the global prevalence of osteoporosis is around 18% with an approximate of 11% difference in favor of men.[13] The reduction of bone mass and bone architecture remodeling result in skeletal fragility and fracture risk.[14] Osteoporotic fractures may lead to complications like thromboembolism, delirium, and challenging pain management.[15] In-hospital stays, outpatient visits, and nursing home stays contribute to increased medical costs in osteoporotic fracture care.[15] Increased morbidity and mortality after osteoporotic fractures[16] highlight the need for prevention, like screening for LBD and introducing prophylactic therapies.

Dual-energy X-ray absorptiometry (DXA) is the gold standard to evaluate bone mineral density (BMD) in the hip, spine, and/or wrist.[13] Based on the femoral neck T-scores, normal BMD is higher than −1.0.[13] The mild form of LBD is osteopenia with the femoral neck T-score between −1.0 and −2.5.[13] Osteoporosis is the advanced form of LBD, with a T-score of $\leqslant -2.5$ measured on the neck of the femur.[13] Advanced age, gender, low body mass index (BMI), genetics, and drugs, like long-term glucocorticoid intake, are the main risk factors for LBD development.[13]

Since no comprehensive evidence describes the relationship of MC with bone mineral decrease, we aimed to investigate whether MC is a risk factor in LBD development and measure the proportion of bone mineral loss in the MC population.

Materials and methods

Our systematic review and meta-analysis protocol was registered beforehand with PROSPERO, which can be viewed using the following hyperlink (registration number CRD42021283392). We outlined our article conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) Statement[17] (Supplemental Table 1), and we complied with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions Version 6.2.[18]

Search strategy

We performed a comprehensive search from inception to October 16, 2021, in five major databases to identify eligible studies: MEDLINE (via PubMed), Embase, Scopus, Web of Science, and Cochrane Library (CENTRAL). We applied our query to all fields/all text (Supplemental Applied Search Keys) in the search engines. No language or other field restrictions were applied.

Eligibility criteria

We included cohort, case-control, and cross-sectional studies. All studies that reported the number of adult patients with MC diagnosed by histopathologic criteria[4] with BMD evaluation were eligible. We had a population (P), exposure (E), outcome (O) (PEO) framework to assess whether MC (E) is associated with the development of LBD, osteopenia, or osteoporosis (O) in adult patients (>18 years) (P).[19] We ascertained the proportion of different bone density diminution and forged our condition (Co), context (Co), population (Pop) (CoCoPop) framework: LBD, osteopenia, osteoporosis (Co) in adult patients (>18 years old) (Pop) in the context of MC (Co).[19]

Study selection and data collection

Our study selection was conducted using a reference management program (EndNote X9, Clarivate Analytics, Philadelphia, PA, USA).[20] Duplicates were discarded automatically and then manually. The reintegrated list of articles was screened independently by the two review authors (AR, MAE): initially based on title and abstract, then by full text. At the sequence of each step, we determined the Cohen's kappa coefficient (κ) to preserve the inter-rater reliability.[21] If disagreements occurred at any phase, we reached a consensus by a third investigator's adjudication (BT). Authors of potentially eligible articles were also contacted in the interest of their results regarding our clinical questions.

For data extraction, we used a predesigned Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA), which two independent authors (AR, MAE) populated with the information. For all studies, we extracted the following information: Digital Object Identifier, first author, publication date – year, country of origin, number of centers, study type, study design, study period, patient characteristics (sample size, age, BMI, percentage of participating females, disease duration), number of patients with LBD, osteopenia, or osteoporosis, number of control cases with the bone pathologies mentioned above, and adjusted odds ratios (ORs) where it was reported. Where the number of patients with LBD was not reported, we added up the number of patients with osteopenia and osteoporosis. We resolved disagreements between the two reviewers through the involvement of a third party (BT).

Quality assessment and quality of evidence

The methodological quality assessment was assigned to two independent reviewers (AR and MAE). To critically assess the risk of bias, we reported The Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies,[22] Checklist for Case-Control Studies,[22] Checklist for Cohort Studies[22] for our prognostic question, and Checklist for Prevalence Studies[23] for our proportional question. In each study's case, we defined the different bias domains and the overall rating as yes/no/unclear or "not applicable." To determine the sample size adequacy, we used a prespecified sample size calculation[24] (Supplemental Formula 1). In the event of any discrepancy between the two appraisers, congruence was attained by a third reviewer's intervention (BT).

We assessed the quality of evidence for our outcomes following the "Grading of

Recommendations, Assessment, Development and Evaluation" (GRADE) Working Group.[25] We used the GRADEPro guideline Development tool[25] to establish the Summary of findings tables (Supplemental Detailed Predefined Criteria).

Data synthesis and analysis

The minimum number of studies required was three to implement the quantitative synthesis. Records without sufficient information for the meta-analytical part (the odds of having osteopenia and osteoporosis in the presence of MC) were integrated into the qualitative synthesis.

A random-effect model was used with an anticipated substantial between-study heterogeneity to calculate pooled effect sizes. We used the Mantel–Haenszel method[26–28] (based on raw data) to calculate the pooled event rate (LBD) for categorical variables and the ORs with 95% confidence intervals (CIs). To pool the calculated ORs with the extracted ORs (where the raw data was not published), the inverse variance weighting method was applied.[29] We applied the random intercept logistic regression model method to compile the proportions for events (LBD, osteopenia, and osteoporosis) with 95% CIs.[30,31] Results were considered statistically significant if $p < 0.05$. Since the number of studies was low (smaller than five), the Hartung–Knapp and Hartung adjustment was not appertained.[29,32]

Between-study heterogeneity was tested with the Higgins and Thompson's I^2 statistics[33] and Cochran Q tests. The I^2 test represented the presence of statistical heterogeneity in percentages across the analyzed studies.[18]

Forest plots displayed the findings of the meta-analytical calculations. Due to the small study number (<10), it was impossible to assess publication bias. The statistical analyses of the data were carried out with R (R Core Team 2021, v4.1.1; Vienna, Austria: R Foundation for Statistical Computing. https://www.R-project.org/) using the *meta*[34] and *dmetar*[35] packages.

Protocol deviation

In order to position our findings, we assessed the ORs for bone density decrease in the MC population compared with age- and sex-matched controls. Due to the limited number of studies in this important field of research, we also included one cross-sectional study.

Results

Systematic search and selection

Figure 1 presents our search process. 3046 records were scrutinized and assessed for eligibility. After screening records identified in five databases, the number of reports assessed for eligibility was 10,[11,36–44] and eventually, three full-text articles[11,36,37] and one conference abstract[38] were chosen for analysis.

Included studies' characteristics

All the analyzed articles in the quantitative and qualitative synthesis were observational studies. A detailed description of their main characteristics is presented in Table 1.

All study participants were older than 35 years, and the female predominance was more than 85% in every article.

The mean disease duration of MC was 4.33 years, where SD was 1.66 years in the Lőrinczy study,[37] while Wildt *et al.*[11] reported a median of 28-month MC disease duration with ranges between 2 and 163. In the case of the Graziano *et al.* study,[36] on average, 399 days passed between the diagnosis of MC and the DXA measurement. The included conference abstract[38] reports neither these data nor sample sizes.

We could obtain adjusted ORs from one article,[36] where authors adjusted results for the following values: BMI, current smoking, current alcohol intake, presence of fracture in the medical history, vitamin D substitution, calcium use, proton pump inhibitor, and steroid use.

Wildt *et al.*[11] reported inhalative steroid use in 14% of MC patients. Budesonide therapy was prescribed in 58% of the MC patients as intermittent use while 30% of them received it as maintenance treatment. Although we have no data on the use of budesonide in the article of Graziano *et al.*,[36] 10.6% of the MC patients received steroid therapy for more than 3-month

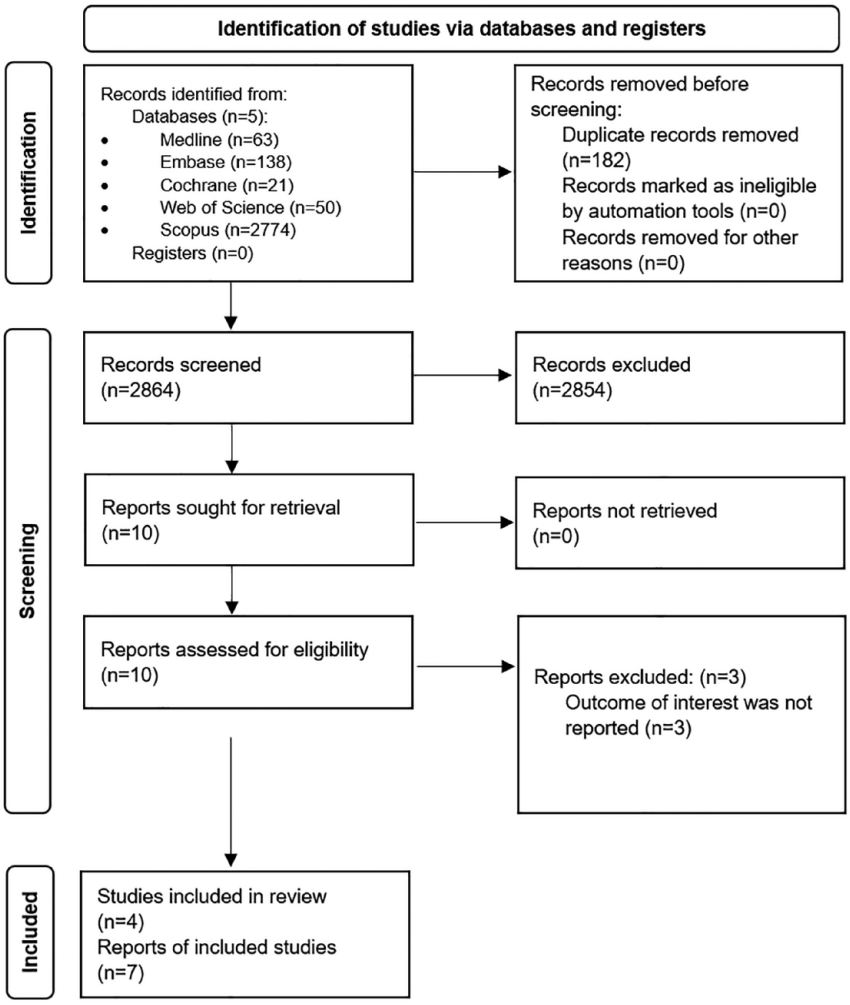

Figure 1. PRISMA 2020 flow diagram presenting the screening and the selection process of the studies.

Table 1. Main characteristics table of the analyzed studies.

Study's first author and year of publication	Study design	Country	Number of patients (N0) MC/CG	Percentage of total female (%)	Age, mean age years ± SD or median (ranges)	BMI (kg/m²), mean ± SD or median (ranges) MC/CG	Smoking history (N0) MC/CG	Steroid use (N0) MC/CG
Graziano 2021[36]	Retrospective case-control	USA	47[$]/188	93.60	63.60 ± 10.70	28.40 ± 6.70/29.80 ± 6.60	24/72[§]	5/10[‖]
Greenberg 2019[38]	Retrospective case-control	USA	94/NA	91	69 (42–91)	NA	NA	NA
Wildt 2018[11]	Prospective cohort	Denmark	50/49	87	67 (45–93)	24 (16–34)/25 (17–34)	17/5	7/1[¶]
Lőrinczy 2011[37]	Cross-sectional	Hungary	14/28[‡]	85.71	49.79 ± 13.06	24.23 ± 7.89/25.34 ± 12.40	5/13	None

[$]They used 118 patients with MC investigating the occurrence of bone mineral changes.
[‡]Matched for age, gender and menopausal state, not just patients with MC but patients with Crohn's disease are compared to matched controls.
[§]Smoking status: current/former/never (current smoker = active smoker at the moment of DXA).
[‖]Prior prednisone >3 months.
[¶]Treatment with inhaled steroids.
BMI, body mass index; DXA, Dual-energy X-ray absorptiometry; MC, microscopic colitis/CG, control group (patients with MC in comparison to age- and sex-matched controls); NA, not available; SD, standard deviation; USA, United States of America.

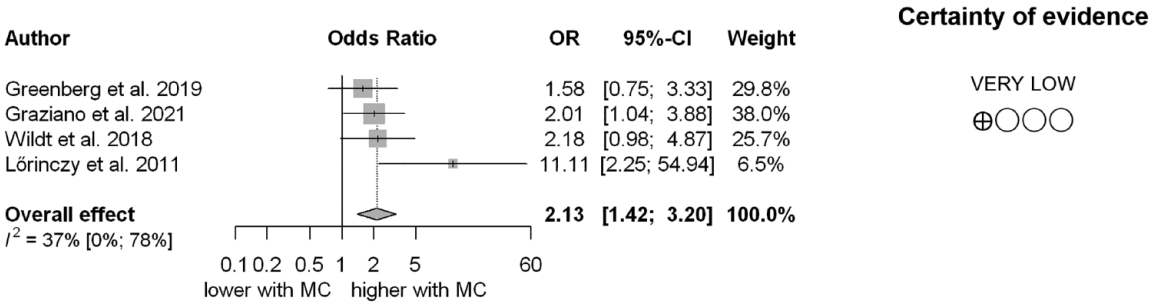

Figure 2. Forest plot demonstrating that MC increases twofold the odds of having LBD.
CI, confidence interval; LBD, low bone density; MC, microscopic colitis; OR, odds ratio.

prior to DXA. None of the MC patients received systemic steroid ever in the article of Lőrinczy *et al.*[37]; however, 79.3% of them have been treated with budesonide in the past, at least 6 weeks before enrollment and for a shorter period than 8 weeks. In the article of Greenberg and Yen,[38] more than two-thirds of the MC patients were treated with budesonide, while no data are available on any other type of steroid use among the MC patients.

Quantitative synthesis

MC as a risk factor for LBD. We included all four articles[11,36–38] into our quantitative synthesis. Each of them used age- and sex-matched controls to evaluate LBD occurrence in patients with MC. As Figure 2 shows, the odds of detection LBD were increased two times (OR = 2.13, CI: 1.42–3.20) in the presence of MC. The I^2 was 37% (CI: 0–78), suggesting moderate heterogeneity across the studies.

As the study of Graziano *et al.*[36] reported an adjusted OR value (OR = 0.83, CI: 0.22–3.15), we performed a separate analysis, including all four studies mentioned above, to see whether it affects our effect estimate. Supplemental Figure 1 also shows a twofold increase in the odds (OR = 2.08, CI: 0.98–4.40) for detection LBD in the presence of MC. The I^2 was 54% (CI: 0–85), suggesting moderate heterogeneity across the studies.

Since the conference abstract[38] did not report on the number of control patients, we made an additional analysis, in which three full-text articles were included.[11,36,37] We analyzed 111 patients with MC; 67 had LBD compared to 265 controls with 110 LBD cases. As Supplemental Figure 2 shows, the odds of having LBD were increased threefold (OR = 2.96, CI: 1.15–7.59) in the presence of MC. The I^2 was 48% (CI: 0–85), suggesting moderate heterogeneity across the studies.

MC as a risk factor for osteopenia. Three studies[11,36,37] reported the presence of osteopenia in patients with MC compared to age- and sex-matched controls. Altogether 111 patients with MC were examined, 54 had osteopenia among them, while in the case of the controls, 87 suffered from osteopenia out of 265. As Figure 3(a) shows, the odds of detecting osteopenia were 2.4 times higher (OR = 2.45, CI: 1.11–5.41) in the presence of MC. The heterogeneity across studies was moderate with an I^2 of 35% (CI: 0–79).

MC as a risk factor for osteoporosis. The same three studies[11,36,37] investigated the prevalence of osteoporosis among patients with MC in comparison to age- and sex-matched controls. Although there was a tendency toward an increase in osteoporosis occurrence, the relationship was not significant (OR = 1.42, CI: 0.65–3.12), and the I^2 was 0% (CI: 0–90), Figure 3(b).

The proportion of BMD reduction in MC. The number of patients with MC included in the proportional analysis was 276, 182, and 182, from which 189, 92, and 20 patients with MC were diagnosed with LBD, osteopenia, and osteoporosis, respectively (Figure 4). Figure 4(a) shows that the overall proportion of LBD was 0.68 (CI: 0.56–0.78), meaning that two-thirds of the MC population had LBD. The I^2 signified considerable heterogeneity with a value of 75%

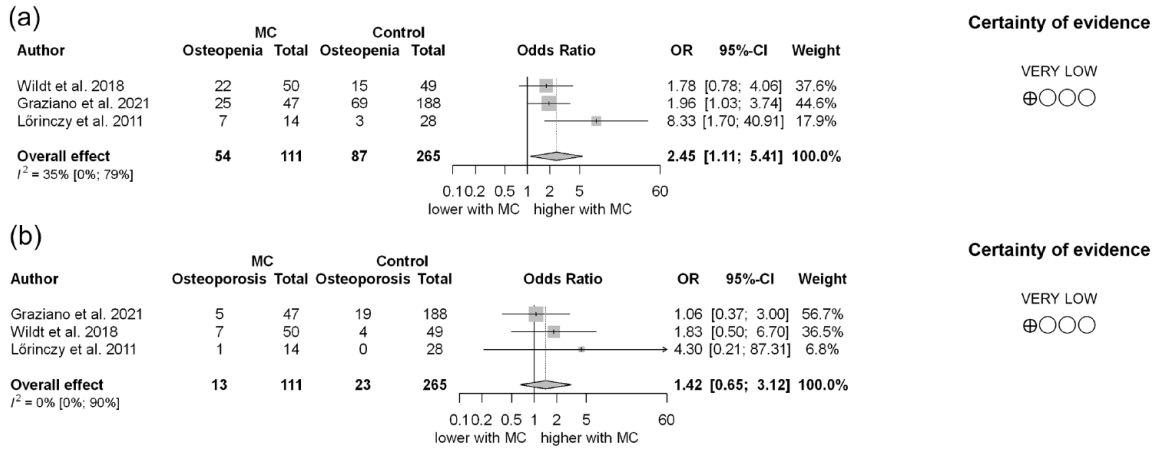

Figure 3. Forest plot demonstrating the odds of detecting osteopenia (a) and osteoporosis (b) in the presence of MC.
CI, confidence interval; MC, microscopic colitis; OR, odds ratio.

(CI: 31–91). Figure 4(b) presents the overarching proportion of the mild form of LBD, osteopenia was 0.51 (CI: 0.43–0.58). Figure 4(c) shows the broadscale proportion of the severe form of LBD, osteoporosis being 0.11 (CI: 0.07–0.16). Half of the patients with MC had osteopenia, and 1 in 10 had osteoporosis. The heterogeneity weighted 0% (CI: 0–90) in these cases (Figure 4).

Risk of bias assessment

Supplemental Figures 3 and 4 summarize the synopsis of the included studies' risk of bias assessment.

MC as a risk factor for LBD, osteopenia, and osteoporosis. All four studies[11,36–38] compared the MC population to controls. However, in every article, the follow-up period of the interested population was missing, and in three cases, no adjustment for confounding factors was reported. All four articles were deemed a high risk of bias (Supplemental Figure 3).

The proportion of LBD, osteopenia, and osteoporosis in patients with MC. All the included studies[11,36–38] were at high risk in the overall appraisal due to the inappropriate patient sampling and small sample size (Supplemental Figure 4).

Quality of evidence. Supplemental Tables 2 and 3 report the Summary of findings tables. In these tables, we collected our outcomes (LBD, osteopenia, and osteoporosis); all of our findings were classified in the very low category on the certainty of evidence ranking list due to the wide variance among the values of ORs, low number of study participants, and measuring a surrogate outcome as BMD.

Discussion

It is well known that gastrointestinal diseases, like inflammatory bowel disease (IBD), celiac disease, gastric bypass surgery, and hepatic diseases lead to secondary osteoporosis .[45–47] It is very important to recognize secondary osteoporosis since the treatment of these patients may be different; moreover, their therapeutic response may vary, if the underlying disease is not recognized and not treated. According to the article of Mirza *et al.*,[48] "up to 30% of postmenopausal women and 50 to 80% of men are found to have factors contributing to osteoporosis." Factors contributing to secondary osteoporosis in gastrointestinal diseases include malabsorption, malnutrition, and/or detrimental drug therapy. In the case of MC, chronic watery diarrhea complicated with stool leakage is a reason for keeping a narrowed diet, leading to malnutrition. MC shows a high association with celiac disease (4.5–6.7%),[49] where malabsorption of vitamin D and calcium can be a further reason for osteoporosis. Moreover, Verhaegh *et al.*[50] showed that 50% of patients with MC display a chronic active or chronic relapsing disease course with chronic diarrhea that might lead to decreased

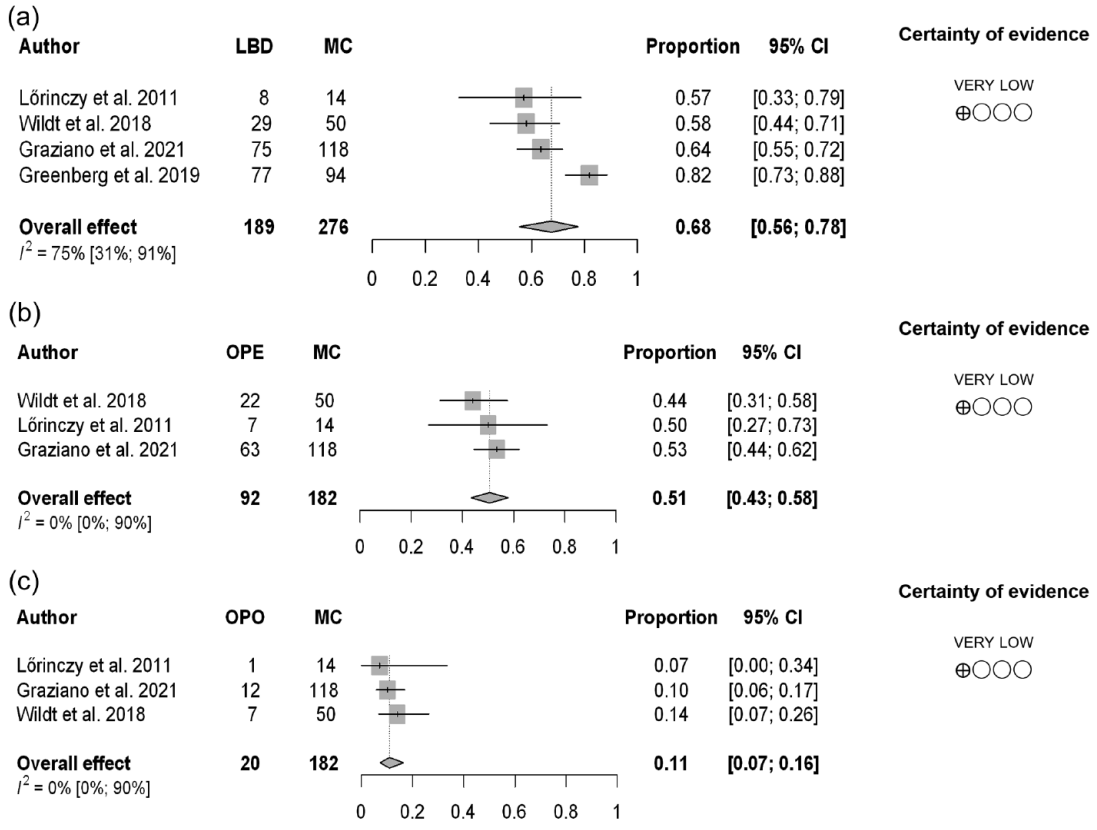

Figure 4. Forest plot presenting the proportions of having LBD (a), osteopenia (b), and osteoporosis (c) in patients with MC.
CI, confidence interval; LBD, low bone density; MC, microscopic colitis; OPE, osteopenia; OPO, osteoporosis.

BMD. Regarding detrimental drug therapy, budesonide – a locally acting steroid – cannot be fully identified as an etiological factor of LBD. At present, there are no data that can lead to timeline conclusions between MC diagnosis and LBD.

This is the first meta-analysis that provides data on the relationship between MC and LBD. This study was conceived from the results of four observational studies[11,36–38] that described the relationship of MC to bone density alterations. We investigated data from four articles[11,36–38] where patients with MC having decreased bone density were compared to age- and sex-matched controls. Our results showed that the odds of having LBD were twofold increased in the presence of MC. When pooling unadjusted ORs with the adjusted ORs from the study of Graziano *et al.*[36] the odds of having LBD were also twofold increased in the presence of MC. When we excluded the conference abstract of Greenberg and Yen[38] due to the lack in number of control cases, data from three articles[11,36,37] showed a stronger association, namely, the odds of having LBD were threefold higher in the presence of MC. Furthermore, we investigated osteopenia and osteoporosis in the context of MC. Our findings showed a 2.4 odd of having osteopenia in the presence of MC; however, in the case of osteoporosis only, an increased tendency was observed in comparison to age- and sex-matched controls. Our comprehensive research provided data on the proportion of bone mineral changes among the MC population as well. Our results showed that two-thirds of the MC population (68%) had LBD. Furthermore, the occurrence of osteopenia was 51%, and osteoporosis was 11% in patients with MC. In comparison, the overall prevalence of osteoporosis was 18% worldwide, determined in 2020.[13]

We found moderate heterogeneity investigating the odds of having LBD and osteopenia in the

presence of MC. This moderate heterogeneity could have been attributed to the presence of the cross-sectional study,[37] which depicted the youngest and the smallest number of patients, in which the bone density of not only patients with MC, but also patients with Crohn's disease was compared to that of matched controls. In the proportional analysis, we detected considerable heterogeneity, which may have been credited to the nature of proportional data, where I^2 is usually high, and even in small sample size studies, little variance is observed.[51] We assume that this considerable heterogeneity might have been explained by the involvement of the conference abstract[38] since it reported on the eldest population with female predominance. Our findings were at a very low level on the certainty of evidence after the GRADEPro guideline,[12,25] partly because the eligible studies used surrogate outcome the BMD. The hardest outcome, osteoporotic fractures, was investigated by the workgroup of Reilev *et al.*,[39] in the context of budesonide treatment in MC. This large nationwide case-control study found no significant association between budesonide therapy and osteoporotic fractures[39]; however, a dose-dependent augmented risk of spinal fractures was demonstrated.[39] One Dutch study supports the use of surrogate outcomes, like examining BMD as a patient-important outcome.[52]

Systemic glucocorticoid is a well-known risk factor for osteoporosis since it stimulates osteoclast activity while inducing osteoblast and osteocyte apoptosis. At the same time, it results in reduced intestinal calcium absorption and elevated calcium clearance through the kidneys. Both mechanisms contribute to the loss of bone quality.[53,54] Budesonide is less detrimental than other corticosteroids and was not associated with increased fracture risk at low doses (3 mg/day).[55] In the induction therapy of MC, 9 mg/day of budesonide is administered, while in the maintenance phase of MC, lower doses of budesonide (3 or 6 mg/day) are used.[4] Regarding anti-inflammatory potential, a daily oral intake of 3 mg budesonide is equivalent to a daily oral dose of 12 mg of prednisolone (more than 5 mg of prednisolone's daily administration causes BMD reduction[56]), although this comparison may not apply to bone cells effects.[55] Recent study by Tome *et al.* published evidence against the budesonide long-term detrimental effect on bone mineral changes.[12] Adverse effects possibly attributed to budesonide-like osteopenia, osteoporosis, hypertension, diabetes, cataracts, and glaucoma were similar in MC patients on budesonide therapy compared to age- and sex-matched MC patients without budesonide treatment.[12] However, numerically twice as many patients with MC developed osteoporosis without budesonide treatment compared to patients on budesonide maintenance therapy.[12] Based on mentioned above, we consider that our data on BMD decrease are attributed to MC and not budesonide adverse effect.

Strengths and limitations

The strength of our study lies within being the first meta-analytical association found between LBD and MC. All eligible studies[11,36–38] used DXA – the cardinal clinical tool to examine skeletal health – to measure BMD.[13] We also applied a robust methodology to all parts of our research, following the PRISMA 2020[17] and the newest Cochrane recommendations.[18] Conversely, this study contains some limitations. We found one eligible conference abstract,[38] which we included in our analysis. Due to the limited number of eligible articles, we pooled together different study types, which may affect our findings. Over and above, we do not have data regarding the included patients daily physical activity; sedentary lifestyle leads to femoral BMD reduction in women.[57]

Implication for research

Further prospective observational studies with long follow-up times should be performed to determine the different prevalence indicators[51] of LBD in patients with MC. Likewise, we would like to highlight the indispensable requirement for incidence studies to elucidate bone density changes and fracture risk in MC. International and national registries, including bone mineral changes, should be established in the near future.

Implication for practice

MC is an underdiagnosed disease, which shows an increasing incidence. We know that it can take years for patients to receive an MC diagnosis. In the meantime, the rate of LBD can increase insidiously. Osteopenia may escalate to osteoporosis, culminating in osteoporotic fractures. For that reason, there is an indispensable demand to take proper measurements in time not to attain this peak. The "European Guidelines on microscopic colitis" do not mention routine screening for

BMD among the MC population.[4] Appraising our findings, we suggest the MC population's screening for BMD at the moment of diagnosis.

Patients with MC may be advised for lifestyle and dietary changes, and calcium and vitamin D supplementation to slow down the LBD development. Impact exercise combined with resistance training best fits for pre- and postmenopausal women to maintain their BMD.[58]

Conclusion

In conclusion, our findings suggest that the odds of having LBD are twofold higher in the presence of MC. LBD and its mild form, osteopenia, was present in more than half of the MC population. Based on our findings, we highly suggest screening patients with MC for BMD at the moment of diagnosis.

Declarations

Ethics approval and consent to participate

No ethical approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct, or interpretation of our study.

The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

Consent for publication

Not applicable.

Author contributions

Anett Rancz: Conceptualization; Data curation; Project administration; Visualization; Writing – original draft.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

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Supplemental material

Supplemental material for this article is available online.

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